Neurology

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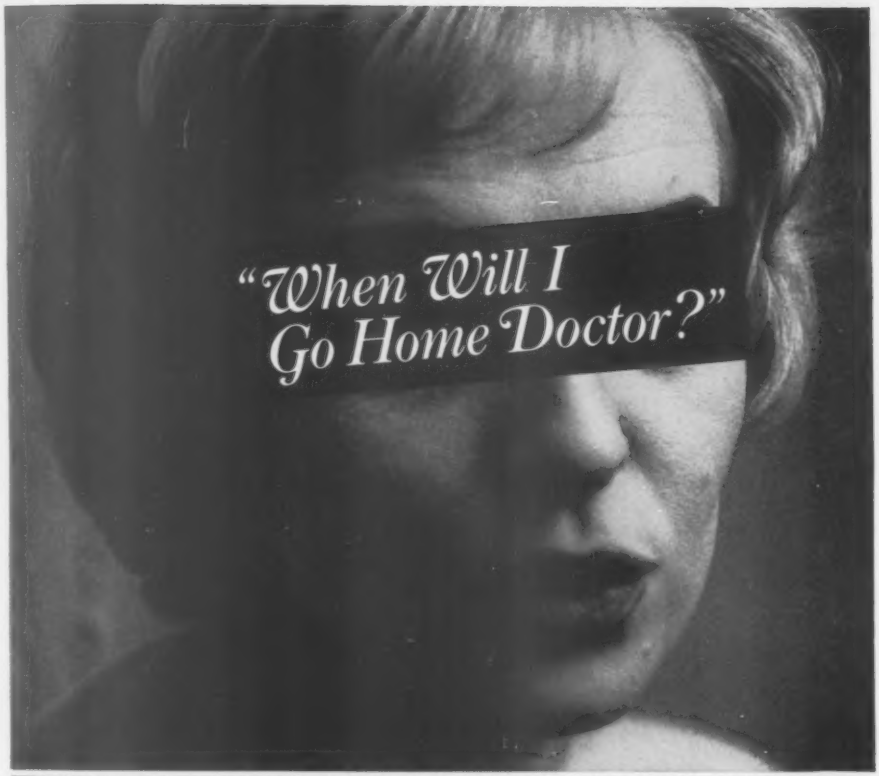

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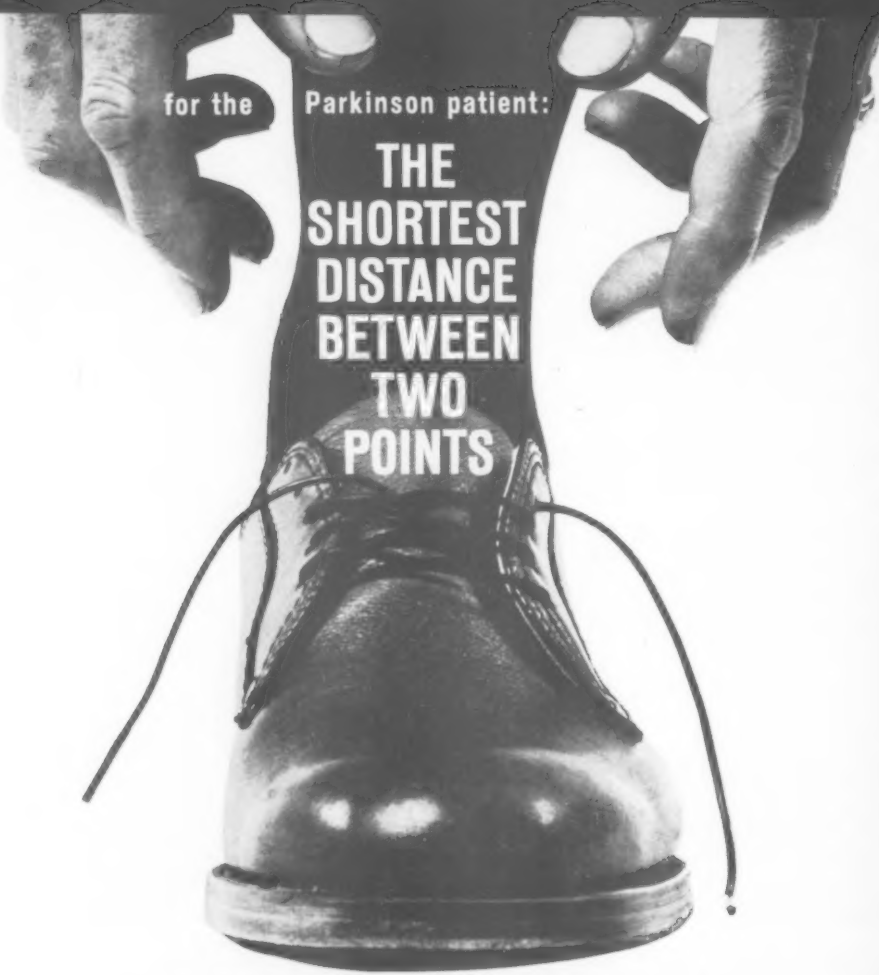

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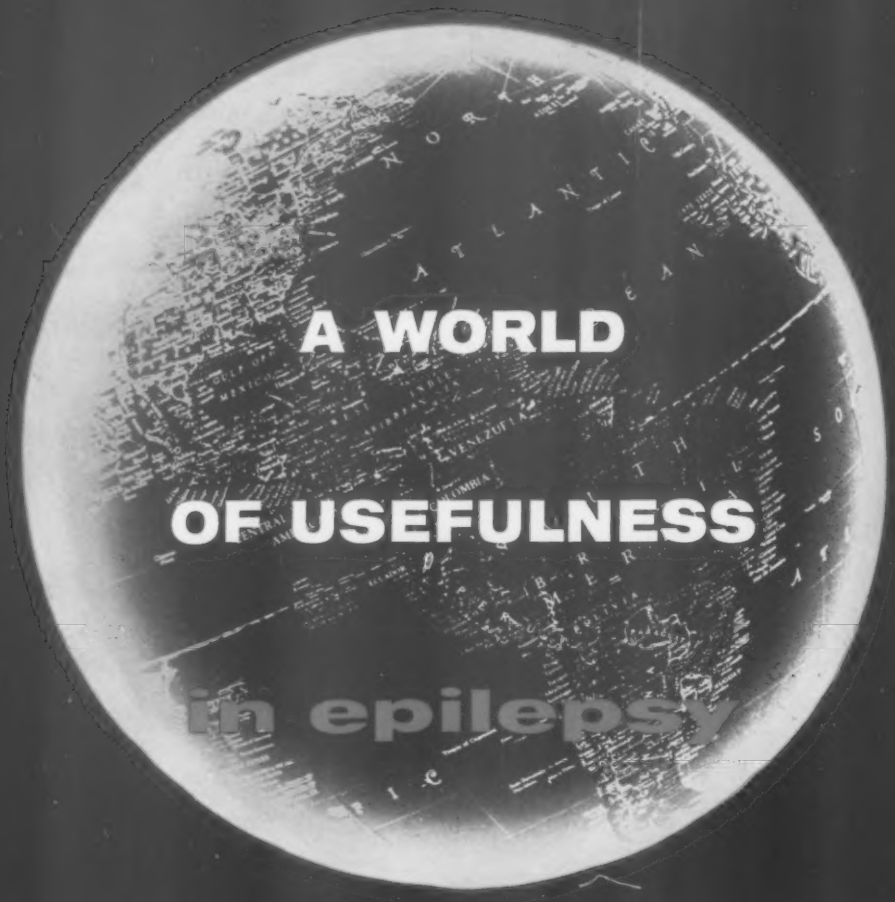

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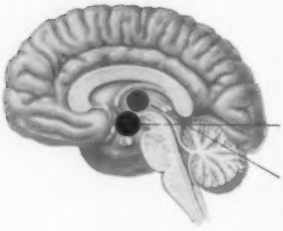

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2. Berger, F.M.: J. Pharmacol. & Exper. Therap. *112*:413-423 (Dec.) 1954.
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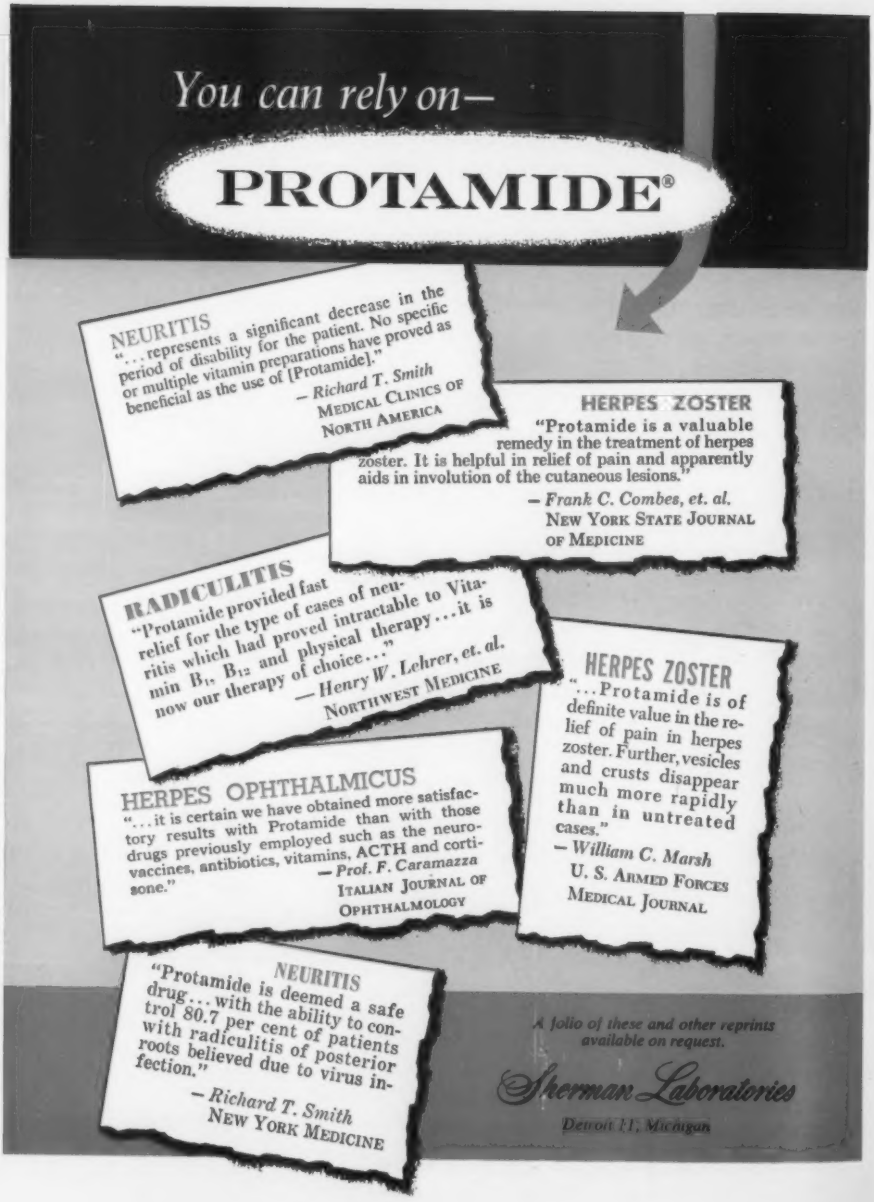
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Anticoagulants for occlusive cerebrovascular lesions

E. F. Vastola, M.D., and A. Frugh, M.D.

CONSIDERABLE EVIDENCE exists to support the view that anticoagulants modify in a favorable manner the natural course of basilar and carotid artery insufficiency syndromes. The experiences of Millikan, Siekert, and Shick[1,2] and of Fisher[3] strongly suggest that, in many patients, the use of anticoagulants may be expected to terminate the episodic manifestations of ischemia which are characteristic of these syndromes.

A decrease in the incidence of irreversible, structural lesions during anticoagulant therapy is also suggested by these authors, but a statistical analysis of the results presents difficulties, and a definitive conclusion should probably be postponed.

The effect of anticoagulants upon the further development of a recent occlusive lesion is another question about which there is insufficient evidence. A favorable effect upon "strokes in evolution" is reported by Fisher,[3] who describes the reversal of a progressing neurologic deficit in 11 of 14 such patients treated. Regression occurred in 5 of 7 patients in whom therapy was stopped or prothrombin times allowed to fall below therapeutic range. In all of 15 fully developed strokes, on the other hand, this author reports no favorable response to anticoagulants. Similarly, Rose[4] and Ushiro and Schaller[5] describe no desirable changes of significance in the course of 24 and 26 patients respectively who received anticoagulants soon after the onset of occlusion. Unfortunately, details concerning the extent of the lesion and time of treatment are not available in the 2 latter reports.

As important as the possibility of preventing further extension of a thrombus is the risk of adding a hemorrhagic component to the infarct already present when therapy is begun. Unambiguous clinical experiences relevant to this point could not be found in the available literature. However, Wood, Wakim, Sayre, Millikan, and Whisnant[6] have shown that the infarcts produced in dogs by the carotid injection of vinyl acetate were more hemorrhagic in both extent and intensity when the injections were followed by anticoagulants in amounts sufficient to maintain the prothrombin times at levels 2 to 2.5 times normal.

One may expect anticoagulants to alter favorably the clinical course of a recent infarct only so far as the course is determined by continued growth of a thrombus either in the vessel initially occluded or in collaterals to the infarcted region. No evidence exists that such continued growth occurs. The possibility that such growth occurs seemed great enough to

From the Division of Neurology, State University of New York College of Medicine, Brooklyn.

TABLE 1
CLASSIFICATION OF PATIENTS

Extent of deficit	*Duration of deficit before therapy*				
	1 *< 12 hours*	*2* *12–24 hours*	*3* *2–4 days*	*> 4 days*	*Total*
A Incomplete	14	9	4	3	30
B Complete	8	4	3	10	25
Total	22	13	7	13	55

justify the use of anticoagulants in the group of patients to be described below. We hoped that observations made in this study would help to answer the following questions:

1] Can progression of the neurologic deficit be halted or reversed by administration of anticoagulants shortly after onset of an infarct?

2] Does regression of a severe neurologic deficit occur more rapidly in the presence of elevated prothrombin times?

3] What is the risk of hemorrhage into infarcted brain during treatment with anticoagulants?

MATERIAL AND METHOD

All the patients used in this study were hospitalized on the neurologic service of Kings County Hospital, New York City. Table 1 classifies these patients according to [1] severity of deficit at beginning of therapy and [2] interval between onset of deficit and beginning of therapy. An attempt was made to treat consecutive admissions having each of the following characteristics:

1] Oeclusive cerebrovascular lesion, thrombus, or embolus without evidence of hemorrhage.

2] Diastolic blood pressure less than 110 mm. Hg at time of admission.

3] Absence of usual contraindications to anticoagulants—tuberculosis, peptic ulcer, and blood dyscrasia.

Administrative difficulties resulted in the loss to this study of many patients who satisfied these criteria, but no deliberate attempt was made to select patients on the basis of criteria other than those above. Ignorance of many of the significant factors in the disease process under study makes it impossible to form a control group as well matched to the group treated as its small size would require for statistical analysis. However, certain generally accepted qualitative expectations exist from which large departures should be obvious. Preliminary comparisons of this kind are particularly important when one of the questions of interest concerns hemorrhage, a potentially dangerous complication of therapy.

The traditional clinical signs were used to distinguish an occlusive from a hemorrhagic lesion. Lumbar puncture was performed on every patient, and, in addition to the usual cerebrospinal fluid studies, a quantitative van den Berg test for total bilirubin was done to rule out that type of intracerebral hemorrhage which does not rupture into the ventricle or subarachnoid space and is represented in the spinal fluid only by an elevation of the total protein and xanthochromia due to bilirubin. Identification of bilirubin in the spinal fluid constitutes unambiguous evidence that intracranial bleeding has occurred, and this finding has been particularly helpful in those patients in whom lumbar puncture was traumatic. A detailed report of our experiences with this determination is in preparation.

Of 55 patients treated, 41 were males and 14 females; the average age was 67.6 years. All patients with hemiparesis were placed in the incomplete category, marked A in Table 1. Some of these patients exhibited, in addition, incomplete hemisensory syndromes, mild dysarthria, or mild dysphagia. This category also includes the 4 patients with basilar system disease, all of whom presented various combinations of brain stem signs. All patients in the

TABLE 2
RESULTS OF THERAPY

	A1	B1	A2	B2	A3	B3	A4	B4	Total A	Total B
Improved	10	2	5	2	2		3	2	20	6
Slightly improved	2								2	
Same	1	2		1	1			6	2	9
Worse	1	4	4	1	1	3		2	6	10

TABLE 3
ONSET OF IMPROVEMENT IN DAYS AFTER BEGINNING OF THERAPY

	Days after beginning of therapy							
	1	2	3	4–5	5–10	10–15	15–20	20–60
A1	3	2			3	2		1
B1			1		1			
A2			1		1	1	1	1
B2				1	1			
A3		1				1		
B3								
A4				1		1	1	
B4					1			1

complete category, marked B, presented solid hemiplegia, in most cases combined with other signs of cerebral involvement. Many had capsular syndrome with hemiplegia, hemisensory deficit, and homonymous hemianopsia plus severe dysphagia. Most of the patients in Category 1 showed clinical progression at least six hours before therapy was begun. In Categories 2, 3, and 4, clinical signs were unchanged for twelve or more hours before start of therapy.

The number of patients with basilar system disease may have been larger than stated. One cannot distinguish with confidence between carotid and basilar system disease in a patient who presents simply unilateral pyramidal tract signs. The former location was recorded in the absence of definite evidence to the contrary.

Electrocardiograms were done on all patients and, in 7, confirmed the clinical diagnosis of auricular fibrillation. However, we question the degree of accuracy with which an embolus may be inferred from coincidental fibrillation and occlusive vascular lesion.

Anticoagulation therapy was instituted for practically all patients with 200 mg. of Depo-Heparin Sodium administered intramuscularly, 50 mg. of heparin sodium administered intravenously, and 75 mg. of Coumadin administered orally. Coumadin was administerad daily thereafter in doses sufficient to keep the prothrombin time at 2 to 2.5 times that of normal controls. Clotting times to follow effects of heparin were not consistently estimated. Prothrombin times were measured daily using Simplastin. Diagnostic plasma was used for normal control times, and this value on most days was eleven or twelve seconds. Our prior experiences with Dicumarol have given us ground for complete agreement with Baer, Yarrow, Kravitz, and Markson[7] who state that Coumadin is a more satisfactory drug because stable levels of prothrombin depression may be far more easily maintained. These authors, in a study of 200 patients, found that a therapeutic range was reached in forty-eight hours in 87% of the patients receiving Coumadin and that 84% of this group were in the therapeutic range at least 70% of the time. In contrast, only 33% of patients receiving Dicumarol were in the therapeutic range at least 70% of the time.

RESULTS

Improvement. Coumadin was given for one to four weeks. Average duration of treatment was two weeks. Table 2 presents the results of neurologic examination of each patient four to eight weeks after therapy was begun. Improved patients presented 50 to 100% remission of their deficit, and slightly improved patients presented 10 to 20% remission. The broad range and clear distinction of these simple categories ensures a classification which would find general agreement. Of 30 patients in the incomplete group, 20 were improved and 2 more were slightly improved, a total of

73%. In the complete group, only 6 of 25, or 24%, showed improvement, and the number who remained unchanged increased. Figures for both the A and B groups are not dramatically different from those expected in any group of patients with occlusive vascular lesions who received only general supportive care. The classification in Table 3 of patients in both A and B groups, according to the interval in days between beginning of therapy and clear onset of recovery, does not reveal the large number of patients in the smaller intervals that might be expected if improvement were obviously related to the use of anticoagulants. However, as improvement in our patients was neither less than expected in degree, nor unduly delayed in appearance, these observations may include small but statistically significant benefits of anticoagulation therapy.

Progression of disease under therapy. The category "worse" in Table 1 means for all patients except 1 increasing coma and death, accompanied, in the case of A patients, by progression of the incomplete neurologic deficit present on admission. The single exception was a patient in the B group whose diagnostic reevaluation prompted by a markedly elevated cerebrospinal fluid protein resulted in the successful removal of a large meningioma. With this exception all of these patients may be considered treatment failures. Prothrombin times in all but 2 showed prolongation in the therapeutic range. In the 2 exceptions, the prothrombin times remained unchanged during the two and four days of therapy prior to death. The response to the initial doses of heparin is not known in these 2 patients.

It is impossible to know, particularly in the B patients, to what extent continued growth of a thrombus or embolus may have been responsible for the progressive neurologic picture, but the mere fact of progression suggests, at best, no great benefit. In only 2 of 16 patients were nonneurologic complications considered the most important factors contributing to death—heart disease in both—although such complications were present to some degree in many. When the prothrombin time was 2.3 times normal, 1 patient very clearly suffered a second occlusive lesion on the twentieth day of therapy. Serial lumbar punctures established the nonhemorrhagic nature of this second lesion.

Possibility of hemorrhage into the infarcted brain tissue is the most interesting question raised in this study. This complication is suggested in the case of 4 patients who died with evidence of bleeding from mouth, rectum, or skin, although no direct proof of bleeding into the brain was found. Direct proof of hemorrhage was obtained in 2 patients, both in the A group. On the seventeenth day of therapy for an occlusive lesion in the right cerebrum, 1 patient had sudden onset of severe headache and paralysis of the right upper extremity. The prothrombin time that day was 2.2 times normal. Lumbar puncture the following day revealed grossly bloody cerebrospinal fluid with a xanthochromic supernatant. The hemorrhagic lesion in this patient seems to have been unrelated to the occlusive lesion present when therapy was begun. The other patient had been started on anticoagulants about six hours after the onset of her occlusive lesion. Lumbar puncture before anticoagulation revealed crystal clear cerebrospinal fluid, a negative van den Bergh test, and protein of 24 mg. per cent. At this time, neurologic deficit was limited to a weakness of the left upper extremity. On the third hospital day, the patient was stuporous and had complete left hemiplegia. Prothrombin time on this day was 2.8 times normal. On the fourth hospital day, stupor was deeper and a lumbar puncture revealed clear cerebrospinal fluid, a negative van den Bergh test, and protein of 225 mg. per cent. Bleeding from the mouth was noted on the fifth hospital day. The patient's neurologic status was unchanged on the sixth hospital day, but bleeding from the mouth continued and gross hematuria was noted. Prothrombin time was 4.2 times normal, and lumbar puncture revealed clear, xanthochromic cerebrospinal fluid, a positive van den Bergh test, and protein of 230 mg. per cent. On the basis of comparison with other patients having a similar course to be described in a later report, we believe the bilirubin present in the cerebrospinal fluid on the sixth hospital day was the result of intracerebral bleeding which had occurred several days before when prothrombin time was still within therapeutic range. The clinical and cerebrospinal fluid

findings are those of hemorrhage into the region of the initial infarct.

Autopsies on 4 of the patients who died provided additional information about hemorrhage. One autopsy, performed on a patient who died twenty-seven days after the termination of treatment, revealed no evidence of a hemorrhagic brain lesion old enough to have occurred during therapy. A second patient, who died five days after termination of therapy because of microscopic hematuria, exhibited a large region of encephalomalacia, a portion of which revealed focal petechial hemorrhages of microscopic dimension. The hemorrhages were old enough to have occurred at the time of stroke or in the first days of therapy shortly thereafter; a more precise estimate could not be made. These hemorrhages seemed small enough to have been able to escape detection in the original cerebrospinal fluid examination and may well have been a part of the original occlusive lesion rather than a complication of the anticoagulant therapy. The brains of the 2 other patients exhibited massive hemorrhagic lesions extending from the lateral convexity of the hemisphere to the ventricular ependyma. The hemorrhages in both patients were estimated to have occurred at least three days after the clinically dated onset of the stroke and during the period of anticoagulant therapy. In both patients, the initial examination of the cerebrospinal fluid revealed no evidence of hemorrhage, and in both patients, rather sudden deterioration of clinical condition occurred during therapy at a time consistent with the development of hemorrhagic extravasation as dated by pathologic examination. Other evidence of hemorrhage caused by anticoagulants is suggested by the microscopic examination of the tissue removed from the patient with the neoplasm. This tissue revealed a highly cellular, well encapsulated, meningocytic meningioma which was hemorrhagic to a degree exceptional for this type of neoplasm.

Relationship between hemorrhagic complications and degree of prothrombin depression. Of the entire group of 55 patients, 36% showed evidence of bleeding in some part of the body, and in only 25% of those bleeding was the complication limited to microscopic hematuria. Table 4 reveals the disturbing fact that, in most of the patients, prothrombin time was in the therapeutic range at the time of bleeding. In only 2 patients was the prothrombin time greater than 3 times the control value.

TABLE 4

PROTHROMBIN TIMES AND SITES OF HEMORRHAGE IN PATIENTS BLEEDING DURING THERAPY*

Prothrombin time			
2	*1*	*0*	*Sites of bleeding*
3.1		>5.2	Hemoptysis
1.1	1.7	1.4	Microscopic hematuria
2.0	2.8	1.7	Mouth
	1.9	1.8	Microscopic hematuria
1.5			Microscopic hematuria, brain
2.3	3.0	2.6	Rectum
2.4	2.5	2.2	Brain
2.8	1.4	2.5	Brain, mouth, gross hematuria
1.7	2.7	2.0	Gross hematuria
2.6	2.5		Skin
2.2	2.3		Hemoptysis
1.9	2.1	1.9	Gastrointestinal tract
		1.9	Microscopic hematuria
2.3	2.2	2.2	Gross hematuria
2.4	1.8	2.0	Microscopic hematuria
1.0	1.4	2.2	Microscopic hematuria
2.2	2.5	2.0	Mouth
2.2	1.6	2.5	Rectum
1.2	2.3	2.1	Skin, brain
3.4	2.7	5.3	Brain

*Prothrombin times given as ratio of patient's value to normal control. Columns 2, 1, and 0 refer respectively to values two days before, one day before, and day of first clinical evidence of bleeding.

Other factors seem to play a role. Neglect of proper mouth care in comatose patients was apt to be followed by bleeding from the mouth and gums. Hematuria in some instances may represent a hemorrhagic cystitis resulting from, or aggravated by, the injudicious use of catheters. However, bleeding into various other of the viscera or into the brain cannot be obviated by even the most meticulous nursing care. The most prominent features of our total group in this connection were the advanced age and generally poor condition of the patients, many of whom exhibited evidence of malnutrition, cardiac disease, or generalized arteriosclerosis. A factor, therefore, which seems to deserve attention is the integrity of the precapillary and capillary components of the vascular system of our patients. It is interesting to note that bleeding occurred in 61% of females and in 24% of males.

SUMMARY

1] Anticoagulants were administered to 55 patients with a presumptive clinical diagnosis of recent occlusive cerebrovascular lesion. No patients were more than slightly hypertensive, and, in all instances, a lumbar puncture prior to therapy revealed no evidence of hemorrhage.

2] With respect to progression of an incomplete lesion, rate of recovery and degree of recovery, the clinical course of these patients was no more favorable than that expected in a similar group treated only by supportive measures.

3] Of these patients, 36% had bleeding in various parts of the body during therapy; this high incidence is not believed to be related simply to the degree of prothrombin depression.

4] It is highly probable that in 4 of these patients, anticoagulation in the therapeutic range was responsible for extensive hemorrhage into the brain with severe deterioration in the patient's subsequent clinical course. In 3 of these patients, hemorrhage occurred in the region involved by the initial occlusive lesion, and, in the fourth, the hemorrhage occupied a different region. The true incidence of this complication may safely be considered to have been higher, since in most patients an adequate search for it was not made.

5] The risk of hemorrhage into the brain appears to contraindicate the use of anticoagulants in the treatment of cerebrovascular lesions under the conditions described in this report.

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Physiologic consequences of total hemispherectomy in the monkey

Operative method and functional recovery

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AT PRESENT, treatment of malignant disease of the brain seldom results in cure.[1] Use of radical surgical procedures for extensive carcinoma in other organs of the body has had some success,[2] but, as yet, this form of therapy has had limited use in patients with infiltrating gliomas and recurrent tumors of the brain.[1,3]

In these patients, the most extensive surgical procedure has been called hemispherectomy, a term that has no precise anatomic definition. The spectrum of anatomic resection included under this operation extends from unilateral decortication[4] to removal of the entire cortex, basal ganglia, and internal capsule from one side of the brain.[3]

Because of the severe neurologic residuals—spasticity, hemiparesis, sensory deficit, and emotional impairment—use of this procedure[3-8] has been restricted. Yet, when one weighs the life expectancy of a patient who has an extensive, infiltrating glioma that cannot be completely removed except by hemispherectomy, the exact degree of mental and physical impairment becomes paramount. In addition, unilateral neoplasms involving the thalamus or subthalamic structures, or both, have been considered inoperable because of the possibility that removal would cause impairment of consciousness or would endanger the patient's life.[3] Thus, the present anatomic limitations of cerebral ablation preclude removal of malignant lesions in the brain.

Few experiments have been performed in animals to test the operative results of hemispherectomy or to define the limits of cerebral resection compatible with maintenance of consciousness and survival. We realize the limitations of applying to man results obtained in experiments on lower animals but felt that investigations of these problems in the monkey, because of its degree of encephalization and comparable nervous system, would be of value.

Excellent studies of hemidecortication and decortication in the monkey have been made by Walker and Fulton,[9] Fulton and Keller,[10] Magnus,[11] and Karplus and Kreidl.[12] Kennard[13] and Fulton and McCouch[14] have been credited with removing the cortex, basal ganglia, and part of the thalamus unilaterally in the rhesus monkey. In 1943, Mettler[15] successfully removed the entire cortex, caudate nucleus, putamen, globus pallidus, thalamus, and subthalamic structures from 1 rhesus monkey. This animal was operated on twice in order to effect total extirpation. The author stated that it is not generally feasible to remove more than the cortex and striatum from the hemisphere of a primate at a single operation.

With the knowledge that 1 monkey had survived hemispherectomy (2 separate operations), we undertook to study the methods and results in rhesus monkeys of complete unilateral removal of all cerebral cortex, basal ganglia, internal capsule, and thalamus at a single operation. We have termed this operation total hemispherectomy.

Abridgment of portion of thesis submitted by Dr. White to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Neurosurgery. Presented in abstract at the Forum on Fundamental Surgical Problems at the meeting of the American College of Surgeons, Atlantic City, October 14 to 18, 1957.

From the Mayo Clinic and Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

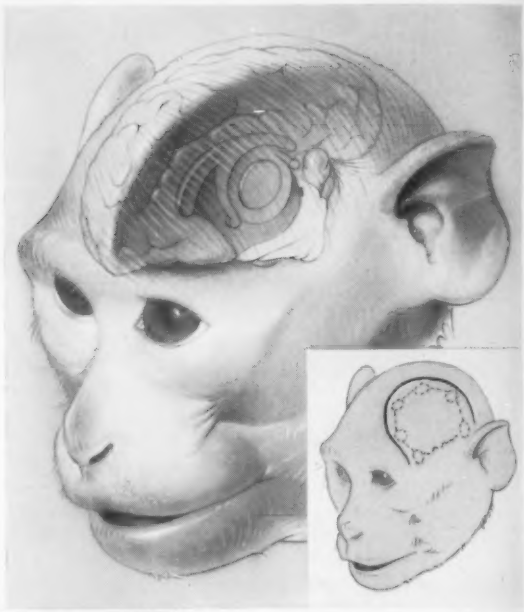

Fig. 1. Artist's conception of totally hemispherectomized monkey. Insert shows skin incision and outline of bone flap.

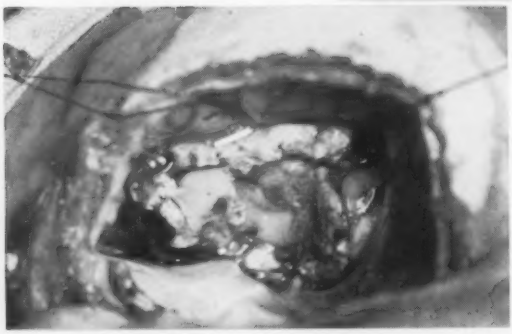

Fig. 2. Photograph taken at operation after removal of left cerebral hemisphere. Note corpus callosum, septum pellucidum, open third ventricle, and anterior commissure. Compare with Figure 1.

The present report deals with the surgical procedure used in such animals and their subsequent functional recovery.

EXPERIMENTAL MATERIAL AND METHOD

In this series, 14 healthy Macaca mulatta monkeys of both sexes weighing 3 to 9 kg. were studied. The series was divided into 3 groups: Group 1, with 9 monkeys that had had total hemispherectomy and were studied extensively for six months or less; Group 2, with 3 monkeys which, after total hemispherectomy and an initial two-week observation period, were allowed to run freely in their cages without handling or examination for eight months to one year, after which a six-month examination was begun (chronic group); and Group 3, with 2 monkeys subjected to unilateral decortication and serving as controls; their examination and care was identical to those of hemispherectomized animals.

The monkeys were examined in specially constructed chairs in which they sat comfortably with their legs hanging free. Studies of

locomotion were carried out in a large cage—large enough to enable the examiner to enter the cage with the monkey.

Careful clinical and neurologic observations were made on these animals before and after operation. Immediately after recovery from anesthesia, the monkeys were examined hourly for eight hours, twice daily during the first week, once daily during the second week, and weekly for six months. Group 2 animals (chronic group) were examined weekly and then monthly during the six-month observation period.

Motor recovery was graded from 0% (no function) to 100% (normal function); tendon reflexes were graded from −4 (no activity) to +4 (extreme hyperreflexia); sensory appreciation, 0% (no response) to 100% (normal response). Only monkeys demonstrating no preoperative neurologic deficits were used.

After sacrifice or death of an animal, a complete necropsy was performed. The extent of the surgical lesion was verified grossly and microscopically. Cinematographic studies were utilized to analyze functional improvement in these preparations.

Operative Procedure (Figs. 1 and 2). After the induction of satisfactory anesthesia with 25 to 35 mg. of pentobarbital sodium (Nembutal) per kilogram of body weight, given intravenously, an aseptic frontotemporoparietal craniotomy was performed. The dura was incised, and the cerebral cortex exposed. No attempt was made to clip or cauterize any vessels before cortical removal. The exposed cerebral cortex was incised with a thin-bladed scalpel to a depth of 2 cm. The incision was made in the form of a cross extending to the limits of the exposed cortex. Immediately the occipital lobe was elevated dorsolaterally and removed, and, in rapid succession, the other portions of the cerebral cortex were removed with a curved periosteal elevator and suction. With removal of the cerebral cortex, the major cerebral arteries were easily visualized and the bleeding was controlled with cautery or hemostatic clips. The various portions of the basal ganglia and the thalamus were carefully dissected free by use of low-pressure suction and sharp dissection. The third ventricle was entered and tissue lateral to the ventricle removed. The anterior commissure, massa intermedia, and septum pellucidum were visualized. The distal limit of the removed brain tissue extended to within 2 or 3 mm. of the superior colliculus. The ventral limit was placed through the subthalamus with attempted sparing of the hypothalamus. When all bleeding was controlled, the cavity was closed dry. The bone flap was wired in place and the wound closed in layers. Great care was taken in closing the skin with a running cotton stitch.

In this operation, no attempt is made to occlude cerebral circulation. Once the hemisphere is removed, the major arteries are easily visualized and bleeding controlled. Interestingly, in all animals, severe vasoconstriction was observed to such a degree that bleeding was often reduced to a minimum even before surgical occlusion was attempted.

RESULTS

All 12 monkeys that had total hemispherectomy survived the initial operative procedure. Of these monkeys, 2 subsequently died of overwhelming infections. Both hemidecorticate monkeys survived operation.

Psychologic evaluation (Figs. 3 and 4). Although no extensive psychologic conditioning or testing was carried out in these monkeys, careful records were kept of their level of consciousness and behavioral recovery.

In spite of the extensive unilateral removal of brain tissue, each of these animals demonstrated early and rapid return of consciousness. Within two to six hours after operation, the hemispherectomized monkey was out of anesthesia and awake, giving evidence of awareness of his environment by noting objects in his remaining homonymous field, avoidance of the examiner, and biting if handled. By twenty-four to forty-eight hours, he would locate and eat an orange section placed near him. Generally, during the first two days after operation, he was irritable, active, and never somnolent. Within two weeks, he began to resume his normal behavioral patterns of eating and grooming, eventually requiring no more care than a normal monkey. As motor function improved, he became investigative, alert, reactive, and aggressive. He would fight with other animals and vie for food. In some instances, he became very clever in escaping from his cage or at the time of examination.

Fig. 3. *(Left)* Macaque, three months after total left hemispherectomy, confined in an examining chair. Note the animal's alertness and awareness. The left arm is being actively raised.

Fig. 4. *(Right)* Monkey that has been subjected to total left hemispherectomy. Note position of flexion of right arm, flexion of right hand, and ease of handling. Monkey has an acrylic electroencephalographic housing unit mounted on skull.

In spite of these accomplishments, a certain plasticity or slowness of reaction was noted in these animals, as if a time lag not normally seen in the unoperated monkey was required between observation and execution.

While it was true that the totally hemispherectomized monkey appeared more docile and more easily handled after operation (Fig. 4), we felt that this docility partially resulted from residual motor weakness, visual impairment, and frequency of handling. In the chronic (Group 2) animals, resumption of normal aggressive behavior and defense reactions characteristic of the untamed rhesus had occurred. Yet the extreme degree of furtiveness and avoidance of persons displayed by the animals preoperatively was never equaled during the period of postoperative observation.

Neurologic evaluation. Motor function: After recovery from anesthesia, the totally hemispherectomized monkeys demonstrated [1] marked contralateral* flaccidity and paralysis, [2] good motor function ipsilaterally,† [3] no evidence of unilateral (ipsilateral or contralateral) decerebrate rigidity, and [4] inability to assume or sustain a sitting posture. While the ipsilateral extremities recovered motor function rapidly from the first day, the paralyzed side exhibited no isolated movement until one day after operation. This movement occurred first at the hip joint.

The animals were able to crawl at two days, to sit by four days, and to assume actual walking posture and gait at one week (the contralateral arm was used as a strut, the leg invariably dragging); when the monkeys were placed on a large vertical screen, they were able to move down at one week, and the majority were able to climb upward by twelve days. Within two to three months, excellent motor recovery had been attained; the totally hemispherectomized monkeys were able to stand without support, walk, run, and climb with excellent agility (Fig. 5).

While the grosser motor activities were carried out well contralaterally, the distal musculature of this side (hand and foot) demonstrated the least recovery (Fig. 6). Yet, although the animals were never able to perform fine tasks with the contralateral hand or foot, both were used to grasp the screen in climbing. This was particularly true of the foot. Both hand and foot generally assumed normal positions during locomotion, but occasionally the hand would be slapped on the floor during running. Reexamination of Group 2 documented the retention of their motor functional attainments.

Spasticity and flaccidity (Fig. 4). Postoperatively, total contralateral flaccidity gradually gave way to limited spasticity. By twelve to twenty-four hours, minimal passive resistance could be detected in the arm which had already assumed a semiflexor posture at the elbow. This resistance slowly increased and appeared greatest two weeks to one month

*Contralateral refers to the affected side, that is, the side opposite the ablated cerebral hemisphere.

†Ipsilateral refers to the side of the body from which the cerebral hemisphere was removed.

Fig. 5. Excellent use of right extremities in climbing is demonstrated in hemispherectomized monkey.

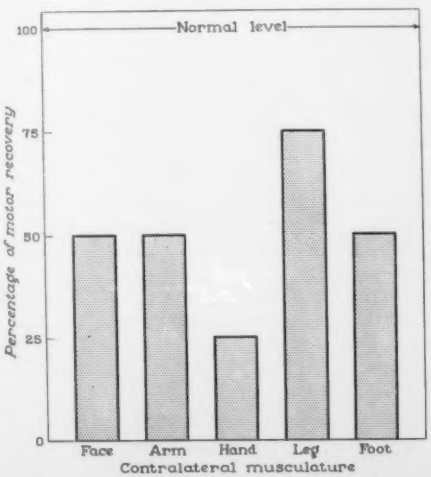

Fig. 6. Recovery of motor function in the contralateral musculature in the totally hemispherectomized monkey.

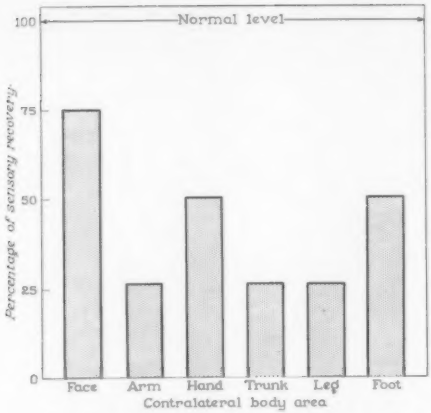

Fig. 7. Contralateral recovery of pain and heat appreciation in the totally hemispherectomized monkey.

after operation. While this resistance to passive motion persisted at the elbow joint, the shoulder was easily manipulated, with the wrist assuming a loose, semiflexed posture. The position of the fingers was variable, ranging from extension – especially when the animals were struggling – to flexion, causing the appearance of an incomplete fist with slight spasticity and simulating a voluntary grasp response when tested.

The lower contralateral extremity remained flaccid, and, although its degree of flaccidity decreased as motor performance improved, the joints remained loose and gave no evidence of spasticity.

Group 2 animals demonstrated moderate spasticity of the affected upper limb, exemplified by passive resistance to extension at the elbow. The contralateral leg remained moderately flaccid.

With struggling, significant increase occurred in muscular tone of the affected limbs and resistance of the joints in all of the totally hemispherectomized monkeys. Clonus was never seen.

Muscle stretch reflexes. After total hemispherectomy in the monkey, the muscle stretch reflexes were depressed. With recovery from anesthesia, a weak contralateral knee jerk could be obtained and was usually graded –2. The ipsilateral knee jerk was more easily elicited during the immediate postoperative period and usually graded 0. Within one week, both patellar reflexes had attained or slightly surpassed their preoperative grading, +1; usually, the ipsilateral patellar reflex had reached this level of activity by four days. Between one and two weeks, the contralateral knee jerk became more hyperreflexic than the ipsilateral, and, generally, this relationship was maintained for the next two to three months during which time the activity of the patellar reflex was at a maximum. Gradually, this reflex pattern underwent modification, for, as the months passed, the contralateral patellar reflex became less active. As a result, the patellar responses were occasionally equal or even reversed in degree of activity.

As a whole, the contralateral and ipsilateral patellar reflexes were found to differ in several important aspects. The ipsilateral reflex required a higher threshold for response, was more brisk, and had a shorter range of motion. The contralateral knee jerk had a lower threshold of activity, and the response was in the form of a slow, wide, pendulous arc.

The inequality of paired reflexes and the persistence of a greater contralateral hyperreflexia were far less striking in the arms than in the legs; frequently, a more active response was obtained ipsilaterally. Examination of preparations one to one and one-half years after total hemispherectomy consistently demonstrated a slight hyperreflexia, more observable contralaterally.

Pathologic reflexes. A Babinski response has been reported in the monkey after section of the cord[10] and also after ligation of the anterior cerebral arteries.[16] Forster and Campbell[16] credit Fulton with obtaining a definite Babinski response in the monkey after hemispherectomy. Examination of the article cited by Forster and Campbell reveals no such finding. Mettler[15] came to the same negative conclusion after reviewing the article.

In none of our animals did a Babinski response develop at any time. Upon plantar stimulation, nonmovement of the toes or foot was the usual contralateral finding, while ipsilaterally a marked withdrawal of the foot with or without plantar flexion of the toes was observed.

Sensory function (Fig. 7). Even in the

healthy monkey, response to a painful stimulus delivered by a sharp pin jab was quite variable. Many of the animals were almost stoic with regard to this type of painful experience, giving no response to the sharpest and deepest of pin jabs. To overcome this problem, a painful stimulus was delivered by squeezing or pinching skin with a surgical hemostat. The degree of pain administered could be controlled, and this method constituted a more painful experience for the animal than did a jab; the animal's response was more constant and varied with the intensity of the stimulus. Degree of pain was evaluated by: [1] degree of withdrawal of the extremity and [2] facial expression and general body response indicating displeasure. While this method leaves some doubt as to exactness, the results in hundreds of examinations were remarkably consistent.

With recovery from anesthesia, the totally hemispherectomized animal with the unilateral thalamus removed was unable to feel severely painful stimulation on the contralateral extremities. In twenty-four hours, the severest of painful stimuli was perceived over the contralateral extremities but was exclusively limited to the face, hand, and foot. Gradual improvement was recorded, until at one month, maximal return of sensory function had been accomplished. The face, foot, and hand consistently demonstrated the greatest recovery; the leg, arm, and trunk, the poorest. Localization was poor and usually limited to recognition of the extremity stimulated. Good localization was observed in the contralateral part of the face.

One other modality of sensation in which contralateral perception was good was heat perception. The degree of perception resembled that of painful pinching of the skin but appeared to be a more painful experience for the animals and to approximate more closely the preoperative levels for hemispherectomized animals.

Ipsilaterally, appreciation of pain and heat was considered normal.

Response to touch and vibration was measurably absent on the affected side. Position sense and hopping and placing reactions also were absent contralaterally.

Our control hemidecorticate animals recovered sensation more rapidly and to a higher degree than did the hemispherectomized animals.

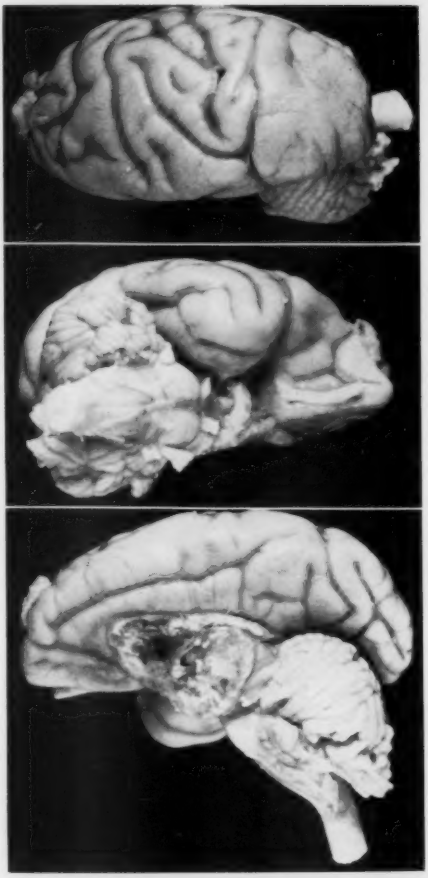

Fig. 8. Gross specimen of monkey's brain after total left hemispherectomy. Dorsal *(top)*, ventral *(middle)*, and medial *(bottom)* views

In 4 monkeys in which the entire left hemisphere had been removed, the right hand was vigorously bitten during periods of painful stimulation, most noticeably when the left foot was pinched. Although this was violently performed at times, no serious injury to the hand was produced. Whittler and associates[17] reported persistent biting of the dorsum of the

hand after production of alumina-cream lesions in the thalamus of a monkey. They have likened this phenomenon to the thalamic syndrome seen in man.

Extrapyramidal manifestations. After total hemispherectomy, no tremor was ever observed under normal conditions in any of the animals. In 4 of the monkeys, handling during the first month after operation caused a sudden, compulsive, jerky motion of the entire body. This manifestation was noted by Mettler[15] in his totally hemispherectomized animal.

Compulsive circling. This phenomenon occurred in all the operated animals. Turning of the head and eyes toward the side of extirpation and circling of the animal toward this side resembled the pattern that develops in an animal from which area 8 of the frontal cortex has been removed.[18] Interestingly, 2 of the hemispherectomized monkeys completely reversed their circling patterns – that is, away from the operated side. This reversal occurred at one month in 1 animal and at an unrecorded time in the other. Once begun, the new circling pattern persisted.

Fig. 9. Section of operated monkey's brain at the level of the thalamus and lateral geniculate body. Note open third ventricle, reduction in left hypothalamus, and absence of left thalamus (Weil's stain, × 6).

COMMENT

To our knowledge, this series of monkeys represents the first group of primates reported in the literature in which the entire cortex, corpus striatum, and thalamus have been extirpated unilaterally during a single operative procedure with the production of an actively functioning animal requiring no more attention after recovery than a normal monkey (Fig. 8).

This technic of cerebral extirpation represents a departure from previous methods of large cortical and subcortical ablation in the primate as reported in the literature. The operative procedures of Fulton and Keller[10] and

Fig. 10. Section through pons of operated monkey's brain showing severe reduction in corticospinal and bulbar tracts (Weil's stain, × 6).

Fig. 11. Section through medulla of same monkey brain as in Figure 10. Note reduction in pyramid and accompanying destruction of fibers (Weil's stain, × 6).

Walker and Fulton,[9] particularly in the production of hemidecorticate monkeys where the major blood vessels supplying the hemisphere are ligated prior to neural excision, closely resemble the surgical technic used in human hemispherectomy.[19,20]

The method of extirpation used in our animals more closely approximates the operative procedure of Bazett and Penfield[21] in the production of bilateral and unilateral decerebrate cats. However, even there, attempts were made to reduce cerebral blood flow by occluding the carotid and vertebral arteries during the actual operation.

Since no attempt is made to reduce cerebral blood flow during total hemispherectomy in the monkey, sole reliance is placed on the normal physiologic mechanisms of controlling blood loss following arterial division. The severe vasoconstriction of the major cerebral arteries occurring during cerebral ablation has been so successful in reducing blood loss that no deaths have occurred at operation. Although 6% dextran is now given in small increments to compensate for immediate blood loss, operation has been successfully performed with only postoperative intraperitoneal fluid replacement.

The recent work of Magoun[22] and French[23] on the so-called activating or ascending reticular system of the brain stem – nuclear patterns of which extend as far forward as the thalamus, subthalamus, and hypothalamus – has demonstrated that chronic lesions in this system result in hypersomnolence and that extensive destruction of this region causes death. Their lesions, however, apparently were bilateral.

Examination of our lesions reveals that portions of the dorsal hypothalamus may not escape resection. Recently, we extended total hemispherectomy to include the unilateral hypothalamus and did not produce hypersomnolence in the monkey. Apparently, as long as the lesion is completely unilateral in its involvement of the anterior reticular system, the elements of consciousness remain intact (Fig. 9).

The excellent restoration of motor function after total hemispherectomy would appear to give credence to the theory of bilaterality of motor innervation (Figs. 10 and 11). While true that somatic responses have been elicited in the monkey from subthalamic and hypothalamic areas[24] and that these areas theoretically could give rise to the purposeful movements on the involved side in the hemispherectomized preparation, the high degree of functional attainment observed would seem to implicate some cortical influence. In the monkey, bilateral movements after cortical stimulation have been elicited by Bucy and Fulton[25] and by Wyss.[26] Bucy and Fulton have located a specific area in the region of the superior precentral sulcus causing exclusively ipsilateral movements. Fulton and Sheehan[27] have demonstrated histologically uncrossed lateral pyramidal tracts in monkeys.

Bates[28] has observed ipsilateral movements upon stimulation of the medial surface of the human hemisphere, and, histologically, an uncrossed pyramidal tract is known to exist in man.[29] Thus the residuals of motor function observed after human hemispherectomy, as in the monkey, could be explained at least in part on the basis of ipsilateral cortical innervation traveling via the direct, uncrossed pyramidal tract. What part the remaining subcortical structures play requires further study.

While the totally hemispherectomized macaque regains a surprising agility in standing, walking, and climbing, no resumption of function for finer movements has ever been seen. The hemispherectomized animal may actively grasp the wire screen with the contralateral fingers or toes, but the contralateral extremities are never used for feeding, picking up objects, or other fine motions. In this regard, the animal differs from the hemidecorticate monkey which may, on occasion, clumsily assist in feeding himself with the contralateral hand. Generally, the hemidecorticate monkey regains motor function more rapidly and to a slightly higher degree than does the hemispherectomized one; however, after maximal return in each animal, the difference is not striking.

At necropsy after hemispherectomy, Austin and Grant[3] have found complete degeneration of the nucleus ventralis posterolateralis of the human thalamus. Yet, while these patients lived, retention of pain was observed. These authors postulated ipsilateral thalamic representation.

Fulton,[30] in discussing the contralateral re-

sidual sensibility in hemispherectomized men and hemidecorticate monkeys, stated that the remaining crude sensation is due to both ipsilateral thalamic representation and residual thalamic function on the operated side.

In the totally hemispherectomized monkey, the unilateral thalamus has also been extirpated. These preparations would seem to answer the problem in favor of ipsilateral sensory representation in the thalamus.

Localization of pain remains poor in the totally hemispherectomized animals except in the face. This excellence of painful reception and localization over the trigeminal area has been documented in man after hemispherectomy.[6] Little difference was found in the degree of contralateral hypesthesia between the hemidecorticate and the totally hemispherectomized monkey. Light touch, vibratory sensation, position sense, and placing reactions were measurably absent in both. This is in general agreement with the findings of Mettler[15] and Walker and Fulton.[9]

A surprising lack of spasticity is seen in the totally hemispherectomized monkey. What spasticity is observed is limited to the affected upper extremity and is manifested by flexion of the upper limb. The lower extremity exhibits no evidence of resistance to passive movement and generally assumes a position of loose extension. Since slight hyperreflexia persists contralaterally and the affected leg is flaccid, findings are comparable to the results of unilateral section of the basis pedunculi in the monkey.[31]

The clinical syndrome of compulsive circling, deviation of the head, and conjugate deviation of the eyes toward the operated side seen after total hemispherectomy in the monkey bears a striking resemblance to the so-called adversion syndrome produced in the monkey by intracarotid injection of the anticholinesterase, diisopropyl fluorophosphate.[32,33]

After unilateral resection of area 8,[18] frontal lobectomy,[18] decortication[13] or hemispherectomy[15] in the monkey, the elements of the above-described clinical syndrome are seen to develop and persist for varying periods.

No explanation, at present, satisfactorily accounts for [1] the diverse means of producing or [2] the multiple areas of the brain causing the adversion syndrome.

CONCLUSION

An entire cerebral hemisphere, including the thalamus, can be successfully extirpated from the brain of rhesus monkeys at a single operation without interference with consciousness and with only moderate reduction in motor and sensory function. The operative procedure and resulting physiologic implications are discussed.

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Congenital muscular hypertrophy

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EVALUATION of muscular disorders in infancy is complex. Infantile disorders associated with hypotonia occur frequently and call to mind a group of diagnostic possibilities, including amyotonia congenita in its neurogenic and myogenic forms, myasthenia gravis, benign congenital hypotonia, different forms of myopathies, brain injuries at birth, and others.[1,2] At the other end of the spectrum, however, is the infant with hypertonicity and hypertrophy of his muscular endowment. Muscular hypertonia without muscular hypertrophy is a physiologic event in the very young infant. Muscular hypertonia becomes of pathologic significance if it persists beyond the third month of life or if it is associated with muscular hypertrophy. This group of diseases will be discussed here along with a review of the literature of congenital muscular hypertrophy and reports of 3 patients who illustrate the diagnostic difficulties.

REVIEW OF THE LITERATURE

The first report of congenital muscular hypertrophy in infants was that of Bruck[3] in 1889. A 10-month-old girl was observed with a large, protruding tongue, large muscles, and hypertonicity. Hypertrophy of the tongue was so prominent that partial surgical removal was done to aid difficult respiration and swallowing. The author described the child as having the appearance of an athlete or wrestler due to the hypertrophied muscular system. In addition to the increased tonicity, the author described pronounced spasms in certain muscle groups. The child died of pneumonia at 19 months. Microgyria was found; unfortunately, complete postmortem examination of the central nervous system was not done. Bruck believed that the muscle hypertrophy was related to abnormalities of the muscle fibers themselves.

A syndrome of congenital muscular hypertrophy, extrapyramidal motor disturbance, and mental deficiency was described in 3 infants by de Lange[4] in 1934. A postmortem description of 1 patient was included. This infant had been observed to have large muscles and hypertonicity at birth. He later was noted to be mentally retarded and intermittently assumed a position of opisthotonus. The child became progressively more rigid and died at the age of 4 months.

Pathologic examination of this patient included many widespread abnormalities. Microgyria, especially of the occipital lobes, was present, and communicating hydrocephalus was noted. The cerebrum was diffusely involved by a large number of small cavities, many of which could be seen on gross examination. Many large glial cells and an absence of ganglion cells characterized the cortex in the region of these cavities. The area normally occupied by the caudate nucleus was replaced by a mass of deeply stained round cells and fringed by large glial cells. Furthermore, ganglion cells were lacking. Cavitation also was observed in the lenticular nuclei and thalamus. In the brain stem, the pyramidal tracts were attenuated and the olivary bodies were abnormal.

De Lange[4] did not express an opinion as to the relationship between the muscular hypertrophy and the alteration in the brain of this infant. However, she suggested that the malformation of the corpus striatum was the primary disturbance and that the multilocular cystic process was a secondary one, attacking an inferior brain. The other 2 patients described by De Lange[4] died at an early age; mental development was therefore not evaluated. Both were underweight and had paroxysmal episodes of opisthotonus.

The following year, Debré and Sémelaigne[5] described 2 infants with diffuse muscular hypertrophy. One child was treated with thyroid

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extract. In six months, her psychomotor development improved remarkably and her muscular status returned to almost normal. The authors reviewed the cases of de Lange[4] and suggested that the muscular hypertrophy may also have been related to congenital hypothyroidism.

Hall and others,[6] in 1936, reported a mentally retarded child with congenital muscular hypertrophy and hypertonicity. As this child possessed a definite increase in muscular strength consistent with enlarged muscles, the authors proposed that the etiology was different from the patients of Debré and Sémelaigne[5] in which the hypertrophic muscles were weak. Excretion of creatine in the urine and alkaline phosphatase values in the serum were increased. These values are opposite to those that are usually found in hypothyroidism.

Middelhoven[7] reported an 11-month-old boy who was microcephalic and underweight and had congenital muscular hypertrophy in addition to macroglossia, hypertonia, and severe mental retardation. Hypertonia and hypertrophy, present at birth, increased in the subsequent months. External stimuli elicited arching of the spine and exacerbation of rigidity. The tendon reflexes were within normal limits. Feeding was difficult because of incessant tongue movements. Thyroid therapy was without effect.

Lecomte and Houet[8] described 2 patients with infantile muscular hypertrophy. The first revealed signs and symptoms similar to Middelhoven's patient: moderate microcephaly, shortness of stature, failure to gain weight, and muscular hypertrophy with macroglossia, hypertonia, and frequent episodes of opisthotonus and idiocy. Thyroid treatment had no effect. The urinary excretion of creatinine and creatine was increased. The inorganic phosphates and alkaline phosphatase in the serum were decreased, but serum calcium and cholesterol were normal. The child died of hyperpyrexia at the age of 11 months; however, autopsy was not done.

The second patient of Lecomte and Houet was one of twins; the other twin was normal. The patient had considerable muscular hypertrophy and hypertonia without tonic spasms. At the age of 4 months, the child weighed only 2,800 gm., was of short stature, and had macroglossia and depression of the bridge of the nose. Although the clinical appearance suggested hypothyroidism, the laboratory findings, in particular the increased creatinuria, did not support this diagnosis. Thyroid medication was instituted and, when 11 months old, the child was mentally and physically normal.

Goldstein's[9] patient was born with an omphalocele which was corrected surgically shortly after birth. At 4 months of age, this child was severely underweight and presented considerable muscular hypertrophy, as well as macroglossia. The mental development of this child was definitely retarded. The pneumoencephalogram revealed cerebral hypoplasia with moderate dilation of the ventricles. The serum cholesterol, inorganic phosphate values, and muscle biopsy were normal.

Further discussion and a case report of congenital muscular hypertrophy appeared in 1955 by Marshall and Hodes.[10] The patient was a premature infant in whom hematuria and large palpable kidneys were noticed in the first few hours of life. At 3 weeks of age, muscular hypertrophy was observed. Thereafter, the child's course was one of deterioration characterized by lethargy, irritability, and episodes of opisthotonus. Normal urinary 17-ketosteroid studies excluded the possibility of muscle hypertrophy from excessive androgenic stimulation. Skeletal roentgenograms, serum cholesterol value, and the general appearance of the infant suggested that hypothyroidism was not present. The child became malnourished and died when 25 weeks old. At autopsy, diffuse muscle hypertrophy, bilateral renal vein thrombosis, and diffuse cystic encephalomalacia were found.

Buchanan[11] has recently reviewed the problem of infantile muscular hypertrophy and has outlined the various types of nervous system abnormalities which can be associated with this finding. He reported a child who, at birth, was found to have a large protruding tongue and excessively developed muscles with little subcutaneous tissue. At 8 months of age, the patient's tendon reflexes were brisk and passive movements of her limbs limited by hypertonicity. Muscle hypertrophy still was pronounced. The child was alert and neither constipated nor anemic. No thyroid medication had been given, although the uptake of

Fig. 1. *Case 1.* Idiopathic congenital muscular hypertrophy in an infant 9 weeks old. Note macroglossia. Diffuse muscular hypertrophy was more pronounced than in the photograph.

radioactive iodine was rather low. Buchanan stated that this entity might be referred to as wrestler's syndrome and that the etiology might become obvious only by observing the child's future course.

CASE REPORTS

Case 1. (P.P., male, born July 21, 1957.) Family history: The child's father was 45, the mother 35. The mother had had 3 stillbirths and 4 normal deliveries. This delivery was a twin birth and occurred in the eighth month of pregnancy, two days after premature rupture of the membranes. The other twin, as well as 4 other siblings, are healthy.

Personal history: Weight at birth was 2,160 gm. The child gained well until, at the age of 8 weeks, one week after an episode of cold and diarrhea, he developed twitching of the hands and rolling back of the eyes. He was hospitalized the same day.

Physical examination on admission: The infant's body weight was 3,600 gm.; height, 52 cm.; and head circumference, 37 cm. The subcutaneous fat was diminished, but muscular hypertrophy and hypertonia were striking. The bellies of the biceps, triceps, forearm muscles, thighs, and calves were so prominent that the child presented the appearance of a miniature wrestler (Fig. 1). The abdominal muscles were less well developed than normal and were rather hypotonic. Flexion of the head often produced an extensor response with arching of the back. A large and continuously protruded tongue was a conspicuous finding. Small umbilical and inguinal hernias were present. Both testicles were descended and pea-sized. All tendon reflexes were excessively exaggerated, and patellar and ankle clonus were readily elicited. Abdominal reflexes, Moro reaction, and Babinski signs were present. The child was able to elevate his head but did not attempt to grasp. He would laugh, fix upon objects with his eyes, and follow light. He had one or more daily bowel movements.

On admission, the limb twitching was believed to be tetanic in origin, as hypocalcemia and hyperpotassemia were found. Despite calcium therapy, however, the muscular hypertrophy, hypertonicity, and hyperreflexia remained unchanged during six weeks of hospitalization.

Laboratory examinations: The admission hemoglobin value was 6.4 gm. per cent. However, this later increased to 9.4 gm. per cent. The reticulocyte count was 10%. The leukocyte and differential counts were normal, and the urinalysis was negative. Ferric chloride test for urine was negative. The spinal fluid was under normal pressure and contained 3 cells per cubic millimeter, a protein value of 74 mg. per cent, and a glucose value of 49 mg. per cent. The urinary excretion of creatine was 7 and 3.2 mg. per kilogram body weight per twenty-four hours; normal is 10 mg.* The value for creatinine was 10 and 19.3 mg. per kilogram per twenty-four hours; normal is 12 mg.* Radioactive iodine uptake was 30 and 40% in four and twenty-four hours, respectively — a reading which is in the upper limits of normal. The protein-bound iodine was 7.4 μg. per cent; normal is 3.5 to 8 μg. per cent. A muscle biopsy was normal. The electroencephalogram was normal for his age. A pneumoencephalogram revealed slightly dilated ventricles and a cavum veli interpositi.[12] The third and fourth ventricles were normal. Roentgenograms of the lower extremities revealed normal bony development and considerably increased soft tissue masses, particularly in the thighs.

Blood chemistry findings during the child's hospitalization are recorded in Table 1.

A follow-up examination of the child at 6 months of age found him to be nearly normal. No further twitching episodes or other spells had occurred. The baby was able to sit up and could stand with support. His body length was 65 cm.; weight, 7,200 gm.; head circumference, 45 cm.; and anterior fontanel, 30 by 20 mm. The child's mental development seemed normal for his age. Evidence still existed of muscle hypertrophy and hypertonicity. The deep tendon reflexes remained somewhat exaggerated, and Babinski signs were present.

At 11 months, he could walk with support and could say a few words; 8 incisors were present. The muscle mass was normal, and the reflexes were not exaggerated. Babinski signs were negative. The child's mother believed that his mental and

*We are indebted to Dr. G. Stearns for providing normal values of creatine and creatinine excretion at different age groups.

TABLE 1

BLOOD CHEMISTRY IN CASE 1

Date:	9–15–57	9–16–57	9–20–57	10–3–57	10–21–57	1–31–58
Age in days	56	57	61	74	92	194
Serum calcium (mg. per cent) Normal: 9 to 11	8*	9.8	9.6	10	10.2	8.8
Inorganic phosphorus (mg. per cent) Normal: 4.5 to 6	6.6	6.6	7.4	7.4	7.6	7.4
Potassium (mEq./l.) Normal: 3.5 to 5	6.2	5.4	5.2	5.2		
Magnesium (mEq./l.) Normal: 1.8 to 2.2	2.2					
Glucose (mg. per cent) Normal: 65 to 100	72					
Alkaline phosphatase (Bodansky units) Normal: 4 to 10		4.3		2.4	4.2	

*Calcium therapy was given from September 15 through October 3. The hypocalcemia on admission is unexplained. Throughout the period of observation, the inorganic phosphates were increased; it is unlikely that the hyperphosphatemia was due to a decreased glomerular filtration since blood urea nitrogen and serum creatinine were within normal limits. The low alkaline phosphatase in this case does not indicate hypothyroidism since the specific tests (protein-bound iodine and I^{131} uptake) were normal. Sodium, chlorides, and CO_2 combining power were normal.

physical development was more advanced than that of his twin.

In summary, a twin baby revealed considerable congenital muscular hypertrophy, hypertonia, hyperreflexia, and macroglossia. This condition was noted when the patient was 2 months old and was studied intensively for a period of six weeks. At the age of 11 months, he appeared normal in all respects, having had no therapy except oral calcium for several days.

Diagnosis: Idiopathic, benign congenital muscular hypertrophy.

Case 2. (T.P., male, born December 3, 1957). Family history: The child's mother had febrile convulsions as an infant; 1 grand-aunt is diabetic.

Personal history: Pregnancy and delivery were normal; birth weight was 3,460 gm. During the first two days of life, the baby received ACTH for undetermined reasons. He developed edema and was kept in an incubator intermittently for the first ten days. During this time, the child was irritable, cried excessively, and had frequent opisthotonic episodes. At 8 weeks, he was admitted to this hospital.

Physical examination: Body weight, 4,000 gm.; length, 53 cm.; head circumference, 35 cm. The anterior fontanel measured 20 by 30 mm. Irritability was striking, and crying was almost continuous. Muscular hypertonia and hypertrophy were severe, deep tendon reflexes exaggerated, and Babinski signs positive. Chvostek and peroneal phenomenon were not present. The child was able to raise his head while in the prone position. However, he could perform no other voluntary movements.

Laboratory examination: The urinalysis and blood morphology were normal. The serum electrolytes were normal: serum calcium was 10 mg. per cent, and inorganic phosphates, 7 mg. per cent. The total serum cholesterol was 167 mg. per cent. Serum proteins were 4.4 gm. per cent, albumin-globulin ratio was 3.6 : 0.8. Urinary creatine and creatinine measured 2.5 and 13.8 mg. respectively per kilogram body weight per twenty-four hours. Roentgenograms of the extremities revealed conspicuous, soft tissue masses with normal bony structure.

When the child was seen again at 4½ months, his left eye had increased in size. At 7½ months, his eye had enlarged still further and showed increased intraocular pressure. He was able to raise his head in the prone position and to follow light with the right eye, but he could not grasp objects or sit up. Despite adequate food intake, body weight was only 5,100 gm. and length, 62 cm. Diffuse spasticity, increased tendon reflexes, and positive Babinski signs were present. Frequent episodes of extensor rigidity and arching of the back occurred. However, the muscular hypertrophy had now almost completely disappeared. Laboratory findings now included negative ferric chloride test, a serum calcium value of 10 mg. per cent, and phosphates, 4.8 mg. per cent. The serum protein value was 4.75 gm. per cent with only 2.1% gamma globulin. Protein bound iodine was 6.2 μg., and cholesterol, 210 mg. per cent. The electroencephalogram was similar to a previous record taken at the age of 2 months — diffuse abnormalities in the form of sharp activity during sleep and an absence of sleep spindles over the left hemisphere. Pneumoencephalography revealed moderate dilation of the ventricular system and increased subarachnoid air.

Diagnosis: Initially, we felt that this case was one of congenital muscular hypertrophy similar to Case 1. Later, however, the signs of brain

Fig. 2. *Case 3.* Muscular hypertrophy in a brain-damaged child with mental retardation and extrapyramidal dyskinesia. Note hypertrophy of the biceps and abdominal musculature.

damage became obvious and it was then apparent that here congenital muscular hypertrophy was related to organic brain disease of infancy with associated delay of mental and physical development. Glaucoma and hypogammaglobulinemia were also present.

Case 3. (D.S., male, born May 8, 1958.)

Family history: Noncontributory.

Personal history: The patient was a second child; the older sibling was healthy. The pregnancy had been normal. However, the mother had 2 fainting spells two months before term. Delivery was an uncomplicated breech presentation, and, at birth, a malformation of the baby's legs was observed. The limbs were flexed at the hips and extended at the knees so that the feet were placed in the axillae. Birth weight was 4,000 gm. Breast feeding was started, but because of sucking difficulty, the infant was placed on a formula at 1 month. At 2½ months, regurgitation and further difficulty with feeding resulted in a hospital visit.

Physical examination (3 months): Body weight was 5,500 gm.; height, 58 cm.; head circumference, 39 cm.; and anterior fontanel, 10 by 10 mm. The child was unable to hold up his head, grasp objects, or follow light. His head and face were asymmetric, with some flattening of the right side. Rotatory nystagmus was present, but pupillary reflexes and funduscopic examination were normal. Continuous choreiform movements of the perioral muscles and tongue appeared to make sucking and swallowing very difficult. In addition, the gag reflex was increased. Considerable muscular hypertrophy and hypertonia were present, especially involving the arms and trunk (Fig. 2). The infant's legs were deformed. The tendon reflexes were exaggerated and Babinski and Rossolimo signs were present. The anal and vesical sphincters also were weak. Frequent dystonic-like spasms occurred, with forceful rotation of the head to the right and with stiffening of the muscles of the trunk and arms. These episodes would last for twenty to thirty seconds; during this time, the infant's arms would be maintained in a boxer-like position. Various types of external stimuli, including auditory and tactile, would elicit these dystonic spells.

Laboratory findings: The serum calcium value was 8.9 mg. per cent, and inorganic phosphates, 7.6 mg. per cent. Alkaline phosphatase was 4.1 Bodansky units. The cerebrospinal fluid contained no cells; protein was 34 mg. per cent; glucose, 51 mg. per cent; chlorides, 123 mEq. per liter. Skeletal roentgenograms were normal, but soft tissue masses were evident. Pneumoencephalography revealed mild dilation of the lateral ventricles. Electromyograms of the right deltoid and triceps muscles showed normal potentials, with complete electrical silence at rest. An electroencephalogram demonstrated no established rhythm. Some slow activity in the left occipital-temporal area was present.

Diagnosis: Severe extrapyramidal dyskinesia with dystonic episodes; muscular hypertrophy and hypertonia; mental and physical retardation, with mild internal hydrocephalus; paresis of the anal and vesical sphincters; and malformation of the legs.

DISCUSSION

A review of the literature and analysis of the cases reported here indicate that congenital muscular hypertrophy is by no means a disease entity. This variable pattern has been emphasized already by previous authors.[6,11] Darré and others[13] distinguished the syndrome of Debré and Sémelaigne,[5] or muscular hypertrophy with hypothyroidism, from that of De Lange,[4] or muscular hypertrophy associated with brain disease, and finally congenital myotonia or Thomsen's disease. Buchanan[11] followed a similar pattern of differentiation.

Without doubt, a form of congenital muscular hypertrophy, associated with spastic or rigid states secondary to organic brain disease in infants, exists. Probably, the patients of De Lange,[4] Bruck,[3] Hall,[6] Middelhoven,[7] Marshall,[10] Case 1 of Lecomte,[8] and Case 1 of Debré[5] as well as Cases 2 and 3 of the present series belong to this category. Almost all these patients had paroxysms in one form or another – mostly episodes of opisthotonus – but also dystonic-like spasms, as in Case 3 of

this series. Mental retardation was found in all patients old enough to undergo an evaluation of intellectual capacity. Findings in the pneumoencephalograms or at postmortem examination of the brain were abnormal in those patients in whom anomaly was sought for.[3,4,9,10] Cases 2 and 3 of our series revealed abnormal pneumo- and electroencephalograms. Case 2, which was initially mistaken for a case of idiopathic congenital muscular hypertrophy, presented signs of severe brain damage at the time of the second admission. In Case 3, signs of a severe extrapyramidal dyskinesia appeared at an early age. The mental development was below normal in both children. The prognosis in congenital muscular hypertrophy associated with cerebral disease depends on the underlying cerebral condition. As to the pathogenesis of the muscular hypertrophy in these patients, we might conjecture that constant innervation secondary to release of inhibition of the damaged cortex induces hypertonicity and hypertrophy of skeletal muscles. In patients with feeding difficulties, for instance Case 3, the paucity of subcutaneous tissue may accentuate the appearance of the muscular hypertrophy to some extent, but the clinical picture is entirely different from that seen in the ordinary malnourished child.

The improvement of the muscular hypertrophy in Case 2 of Debré[5] and Case 2 of Lecomte[8] after thyroid therapy suggested to these authors and others,[13] that cretinism was one of the causes of congenital muscular hypertrophy. The macroglossia found in these cases certainly suggests hypothyroidism, although macroglossia has been found in other patients with muscular hypertrophy as well. One cannot overlook the fact that neither the other clinical symptoms nor the laboratory changes were compatible with hypothyroidism in these cases.

The hypercreatinuria in Lecomte's[8] patient was not suggestive of hypothyroidism, since urinary creatine in cretins is usually lower than 4 mg. per kilogram body weight per twenty-four hours.[15] The normal serum cholesterol in this case is not conclusive, since the cholesterol level may be normal or even low in cretins below 1 year of age.[14] Recent investigators[16] do not describe muscular hypertrophy as a sign of infantile cretinism. Poncher and Woodward[17] have "never observed muscular hypertrophy and hypertonia in a large group of untreated hypothyroid children" although it may be found in older cretins.[18–23] The causes of muscular hypertrophy in these patients is not well understood. A possible cause could be hypergonadism which is found in some adult cretins. Papanicolaou and Falk[24] have shown the effect of androgenic hormone in producing general muscular hypertrophy in guinea pigs. In this connection, it might be worthwhile to mention a type of muscular hypertrophy found in cases of adrenogenital syndrome. Here, again, the increased bulk of muscle mass appears later and is not seen in infants. We may conclude, therefore, that there is insufficient evidence to assume that hypothyroidism is a cause of congenital muscular hypertrophy in infancy. However, thyroid medication may have a beneficial effect in some patients with this disease.

Muscular hypertrophy is found also in myotonia congenita,[25] which may appear early in infancy. Myotonia congenita shows a strong hereditary trend; isolated cases are rare. The presence of myotonic phenomena and delayed muscle relaxation helps to distinguish myotonia congenita from other forms of congenital muscular hypertrophy.[26]

Enlarged, firm muscles have been reported[27,28] in glycogen storage disease (muscular glycogenosis). However, hypotonia, muscular weakness, and sometimes cardiomegaly and hepatomegaly distinguish the condition from the previous ones. The histologic demonstration of abnormal glycogen deposition in the muscle fibers confirms the diagnosis.

The cause of muscular hypertrophy in our Case 1 was not evident. The normal development and healthy appearance of the child at the age of 11 months ruled out a severe cerebral disease, although the presence of a cavum veli interpositi raised some initial suspicions of a cerebral malformation. Concomitant malformations are frequently found in cases where air studies reveal a cavum veli interpositi.[12] This child was certainly not a cretin. The clinical appearance and behavior were incompatible with hypofunction of the thyroid, as were the results of the specific tests, such as the determination of the protein bound iodine and the uptake of radioactive iodine. The spon-

taneous improvement without any specific treatment suggests the existence of a benign and reversible form of a congenital muscular hypertrophy. In an early edition of Pfaundler-Schlossmann's "Textbook of Pediatrics," [29] a form of myotonia in early infancy is described which is not mentioned in later textbooks. The condition is considered to be an exaggeration of the physiologic hypertonia of the young infant. Like physiologic hypertonia, this myotonia in infancy disappears after a few months and is therefore considered a benign form of myotonia. The cause is unknown. Possibly, our Case 1 is a particularly pronounced example of this condition which might be called benign or reversible idiopathic congenital muscular hypertrophy.

SUMMARY

The cases of congenital muscular hypertrophy reported in the literature are reviewed and 3 new cases are presented. Evidently, several different categories of congenital muscular hypertrophy in infancy must be distinguished.

1] Congenital muscular hypertrophy associated with brain disease

2] Thomsen's disease or myotonia congenita

3] Muscular glycogenosis

4] Benign idiopathic congenital muscular hypertrophy

Although previous authors have indicated that hypothyroidism may be one of the causes of congenital muscular hypertrophy, recent experiences cast some doubt on the existence of such a relationship. Thyroid medication, however, may have a beneficial effect on certain patients with muscular hypertonia and hypertrophy in infancy, but reasons for this effect are not clear.

It is hoped that the above reported cases and discussion will stimulate further interest and investigation of this problem.

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Ethoxzolamide—a new anticonvulsant

Seymour Solomon, M.D., and Asao Hirano, M.D.

DURING THE PAST two decades since the discovery of Dilantin, anticonvulsant medications have become available in ever greater numbers; there are approximately 12 in general use at the present time. With each new medication, a number of poorly controlled patients have had seizure frequency significantly reduced. As the number of patients who cannot be controlled grows increasingly smaller, the standards of effectiveness for anticonvulsant agents become more stringent. New medications, to be of practical value, should significantly decrease the frequency of seizures in patients who had not been controlled with presently available medications. The administration of a new compound, ethoxzolamide, to poorly controlled seizure patients has resulted in sufficient benefit to warrant this preliminary report.

Ethoxzolamide, 6-ethoxybenzothiazole-2-sulfonamide, is a carbonic anhydrase inhibitor of the sulfonamide group (Fig. 1). As noted by the chemical structure, ethoxzolamide is related to acetazolamide (Diamox). It has been shown[1] that the anticonvulsant properties of acetazolamide are due primarily, if not solely, to its action as a carbonic anhydrase inhibitor. Moreover, the anticonvulsant properties of this compound are in direct proportion to the degree of carbonic anhydrase inhibition it effects in the brain. It would be logical to assume, therefore, that a more potent carbonic anhydrase inhibitor would have greater anticonvulsant action.

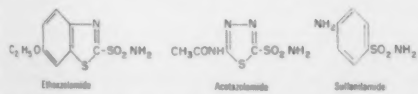

Fig. 1. Formulas of three anticoagulants in the sulfonamide group

The potency of ethoxzolamide in inhibiting carbonic anhydrase was found to be twice that of acetazolamide in vitro.[2] In clinical trials for treatment of glaucoma,[3] ethoxzolamide, presumably by its action as a carbonic anhydrase inhibitor, was found to be approximately double the potency of acetazolamide. Studies of congestive heart failure[4] have noted an increased effectiveness of ethoxzolamide as a diuretic when compared to acetazolamide. Ethoxzolamide has been found[5] more effective than acetazolamide but less effective than Dilantin in protecting rats against electroshock activation. These preliminary data prompted our trial with this new compound.

MATERIAL AND METHOD

The impracticality of ideal control studies, for example, double blind technic, in dealing with major seizures is obvious. We have used our patients as their own controls, comparing their course before the trial of the new medication with the clinical course after such treatment. The problem in evaluation caused by the spontaneous variability in seizure frequency was largely overcome by averaging seizure frequency during one year before onset of the trial medication and indicating the maximum and minimum frequencies during that time. As of May 1958, observation of patients after ethoxzolamide administration has been made for six to seventeen months, with most patients having been observed for the greater period of time. To stabilize as many factors as possible and because of the fear of status epilepticus, the basic medication being taken by the patient – usually Dilantin and phenobarbital – was not altered. Since other newer

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Ethoxzolamide was supplied as Cardrase by the Upjohn Co. of Kalamazoo, Michigan.

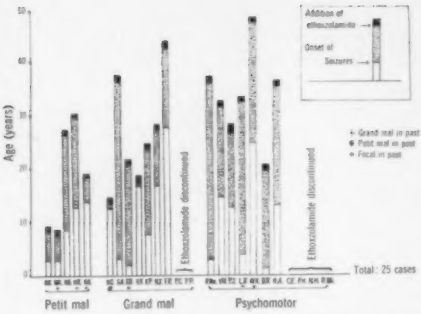

Fig. 2. Data on the 25 poorly controlled epileptic patients included in this study

commercially available anticonvulsant agents had not altered seizure frequency when added to the basic regime, improvement which occurred with the new compound was presumed to be significant. Because of the difficulties of discontinuing all previous medication, maintenance of the basic anticonvulsants while adding the trial drug has been an accepted procedure.[6,7] Other measures of the degree of effectiveness, such as gradually withdrawing the basic anticonvulsant while adding the new compound, in better controlled patients where the danger of status epilepticus is a lesser factor, and studying previously untreated epileptics are not a part of the present report. Such studies are now in progress. The possible psychologic benefit that comes from starting a new medication was discounted because a study of the past records of our poorly controlled patients failed to reveal significant change with administration of other new medications and because of the duration of our follow-up studies. Although change in the severity of seizures is not usually considered a factor in the evaluation of a new anticonvulsant compound, changes were considered important when a reduction in severity was of practical significance.

In choosing poorly controlled patients for this study, we arbitrarily defined poor control as the occurrence of more than one seizure per month in spite of trials on appropriate anticonvulsant medications. The frequency of petit mal seizures was estimated per day. The frequency of psychomotor and grand mal seizures was estimated per month, but no more than one seizure per day was tabulated. As noted above, in the majority of these patients, trials with virtually all of the commercially available anticonvulsants had been made without success. The initial dose of ethoxzolamide was 125 mg. administered once or twice a day. This was quickly increased to an average daily dose of 375 mg. and gradually increased thereafter. A maximum of 750 mg. per day was administered to a few patients.

Of the 25 patients of the Montefiore Hospital Epilepsy Clinic studied (Fig. 2), 5 had petit mal, 9 grand mal, and 11 psychomotor seizures. Although 11 patients had a past history of more than one type of seizure, only a single type had been recurring in all patients during the period of our study. Medication was discontinued in 2 patients with grand mal convulsions because of side reactions and in 4 patients with psychomotor seizures because the validity of their reports was very questionable. The patients' ages ranged from 8 to 48, with adults greatly predominating. The patients were initially observed at weekly intervals; the intervals were gradually extended to one to two months. All patients had previously been evaluated with electroencephalography, blood chemistries, and other appropriate studies. The electroencephalogram, blood count, urinalysis, and blood urea nitrogen determination were repeated during the administration of ethoxzolamide.

RESULTS

The results are tabulated in Figure 3. Complete or excellent control was defined as absence of seizures in patients with grand mal or psychomotor epilepsy and as an average of one or less seizures per day in patients with petit mal epilepsy. The altered criterion for the petit mal seizures was deemed justifiable in view of the striking reductions of seizure frequency that this degree of control represented. Significant response was defined as a drop in seizure frequency of 50% or more, any other effect as insignificant or poor response.

Of 5 patients with petit mal, 4 had excellent control and 1 had insignificant control. Complete control resulted in 5, significant control in 1, and insignificant or poor response in 1 of the 7 patients with grand mal seizures. Of 7 patients suffering from psychomotor epi-

lepsy, 1 had complete control, 3* had significant control, and 3 had insignificant or poor control.

Of those classified as insignificant responses, it is of interest to note that the 1 patient having grand mal seizures and 2 of the 3 patients having psychomotor seizures had a prominent reduction in the maximum seizure frequency. One patient (U.C.) with grand mal seizures, who had had petit mal in the past, experienced complete control of the grand mal seizures but noted a return of one or two petit mal attacks per week. Although the number of patients involved in this study is inadequate for statistical evaluation, it would appear that ethoxzolamide is most effective in patients with petit mal and grand mal, less effective in those with psychomotor seizures.

TOXICITY

Side effects were present in 13 of 25 patients. Laboratory data failed to reveal significant change in the blood count, urinalysis, blood urea nitrogen, or electroencephalogram. The most common untoward symptom was dizziness; 6 patients were affected. Drowsiness was noted by 3 patients. Scattered aches or peculiar feelings, especially in distal portions of extremities, presented in 2 patients, and 2 patients reported headaches. In 1 patient, an unusually soft stool was noted but diarrhea was not present. Side effects noted by other authors[3,4] such as other gastrointestinal disturbances and weakness were not complained of by our group. In only 2 patients were the symptoms of a degree which required discontinuation of the medication. In all other patients, symptoms subsided upon continuation of medication.

DISCUSSION

The mechanism of action of ethoxzolamide is presumed to be the same as that of acetazolamide – a carbonic anhydrase inhibitory effect. This inhibition is related to the SO_2NH_2 complex of these sulfonamides. The direct association between carbonic anhydrase inhibition and anticonvulsant properties was demonstrated by Millichap, Woodbury, and Goodman.[1] Using nephrectomized mice, they proved that the anticonvulsant properties of acetazolamide were not related to the diuretic or acidotic potentialities. Moreover, they found the anticonvulsant effect was increased in direct proportion to the carbonic anhydrase inhibition

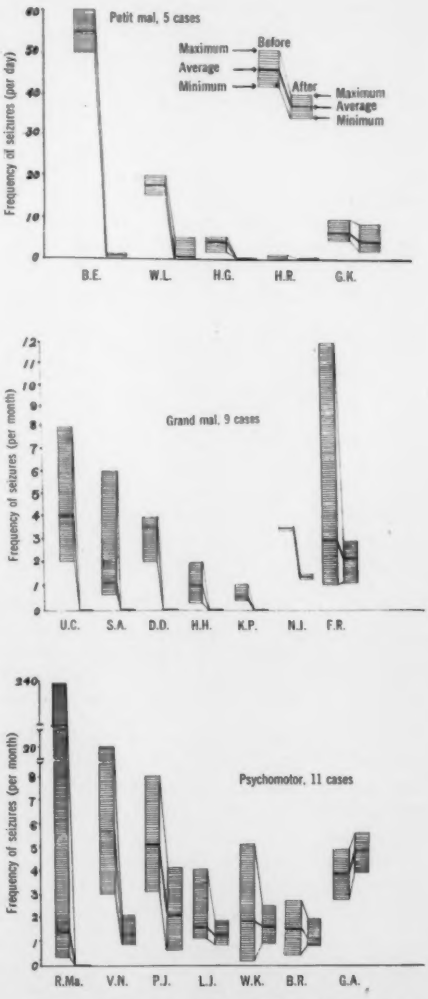

Fig. 3. Results of ethoxzolamide therapy in patients with petit mal, grand mal, and psychomotor seizures

*Included in this count was 1 patient (B.R.) who was significantly controlled in that seizures which had been extreme and socially unacceptable had been so attenuated that only the patient was aware of a momentarily altered state of consciousness or behavior.

when comparing a weak carbonic anhydrase inhibitor, sulfanilamide, to the more potent acetazolamide.

The relationship between carbonic anhydrase inhibition and depression of convulsive activity is thought to be due to the accumulation of carbon dioxide in the brain. It is known that the enzyme carbonic anhydrase accelerates the reversible reaction of $CO_2 + H_2O \rightleftarrows H_2CO_3$. The inhibition of this activity may delay removal of the carbon dioxide which develops in association with neuronal activity. Since carbon dioxide depresses the speed of nerve conduction and increases the electrical threshold, its presence would tend to delay the return of nerve sensitivity after neuronal discharge. In support of the above, it has been shown[8] that carbon dioxide potentiates the anticonvulsant effect of the carbonic anhydrase inhibitor, acetazolamide. The potency of this particular group of anticonvulsant agents appears to be dependent upon the degree of carbonic anhydrase inhibition and, of course, upon the degree of concentration in the brain. Millichap and associates[7] emphasized the extreme importance of the latter factor. They revealed that although potency of enzyme inhibition of acetazolamide in vitro when compared to sulfanilamide was 100:1, the ratio of concentration in the mouse brain at the same dosage level was approximately 1:50. Consequently, the effective carbonic anhydrase inhibition in the brain and anticonvulsant effect were in a ratio of only 2:1.

We do not have knowledge of the concentration of ethoxzolamide in the brain, but its high potency as a carbonic inhibitor most probably accounts for its effectiveness as an anticonvulsant in our series of poorly controlled epileptic patients.

SUMMARY

The anticonvulsant effect of a new carbonic anhydrase inhibitor, ethoxzolamide, was studied. In a group of 25 epileptic patients who had been under poor control in spite of trials on virtually all commercially available anticonvulsant agents, 19 were found suitable for prolonged study over a seventeen-month period of time.

Most patients with grand mal and petit mal seizures were brought under excellent control; the improvement of patients with psychomotor seizures was significant but less striking. Side effects necessitated termination of treatment in 2 of 25 patients, but toxic effects in the remainder were minimal. Because of its high potency as a carbonic anhydrase inhibitor, ethoxzolamide appears to be a significant addition to the growing number of anticonvulsant agents.

The authors wish to thank Dr. Shukuro Araki for help in initiating this work and Dr. Tiffany Lawyer, Jr., for his assistance in the development of the project and in the preparation of this manuscript.

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Treatment of narcolepsy with Ritalin

Robert E. Yoss, M.D., and David Daly, M.D.

In 1956, we reported favorably on the use of methyl phenidate hydrochloride (Ritalin hydrochloride)* in the treatment of narcolepsy.[1] This preliminary report described the results of therapy in 25 patients with narcolepsy who were treated from one to six months. Of these patients, 84% reported good to excellent relief of their abnormal sleepiness. Encouraged by these results, we have continued to use the drug. The present report is based on a study of 60 patients – including most of the original 25.

NATURE OF STUDY

In the interval from April 1956 to November 1957, we had prescribed Ritalin for 68 patients; however, at the time of final evaluation, adequate information was lacking about 8. Patients who reported good or excellent results took the medicament for eight to twenty-seven months. Most of the patients who reported poor results took the medicament for only a short time. Of the 60 patients, 43 were males and 17 were females. They were 12 to 67 years old. The condition of these patients fulfilled the criteria for the diagnosis of narcolepsy elaborated elsewhere.[2]

All patients in this study were seen by one or both of the authors. Each patient was shown how to use the drug and told the goal of the therapy. The patients were asked to remain in Rochester for a few days of initial treatment so that the immediate results – including side effects – could be observed. The use of all other medicaments was discontinued. The beginning dose for most adult patients was in 20-mg. tablets; patients were instructed to take 1 tablet approximately thirty minutes before each meal. Subsequently, the dosage schedule was altered, depending on initial response. As a rule, patients were asked to increase the quantity of the drug until symptoms were relieved or undesirable side effects developed. Final dosage schedules were not determined until the patient had returned to his usual job and environment. Follow-up data have been derived from correspondence with the patient and relatives, from return visits to the clinic, and from a formal questionnaire sent to all patients.

Initially, we made comparative trials of Ritalin, dextroamphetamine sulfate (Dexedrine sulfate), and pipradrol hydrochloride (Meratran). We abandoned this technic when it became apparent that most patients preferred Ritalin. Subsequently, the treatment of all patients began first with Ritalin. Other analeptic agents were used only if Ritalin proved unsatisfactory. Of the patients, 43 have had experience with the effects of one or more analeptic agents in addition to the effects of Ritalin. These agents included amphetamine, dextroamphetamine sulfate, ephedrine, methamphetamine hydrochloride, and Meratran. In addition, a number of patients had been treated previously with desiccated thyroid extract or with anticonvulsant drugs; however, in our experience, these latter medicaments are ineffective in the treatment of the narcoleptic tetrad.

RESULTS

We classified the result of therapy as excellent when the patient reported 75 to 100% relief of the symptoms. If 50 to 74% improvement occurred, we called the results good. Results were classified as poor if less than 50% improvement occurred, if the patient preferred another analeptic agent, or if side effects were intolerable.

Excellent results were reported by 34 patients from the use of Ritalin for relief of their

*We wish to express our appreciation to Ciba Pharmaceutical Products, Inc., for generously supplying the methyl phenidate hydrochloride (Ritalin hydrochloride) used in this study.

From the Mayo Clinic and Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

TABLE 1
USE OF RITALIN

Results	Narcolepsy Patients	Narcolepsy Per cent	Cataplexy Patients	Cataplexy Per cent
Excellent	34	57	9	33
Good	15	25	6	22
Poor	11	18	12	44
Total	60		27	

TABLE 2
USE OF RITALIN:
SIDE EFFECTS IN ORDER OF FREQUENCY

Nervousness
Anorexia
Insomnia
Tachycardia
Skin rash (rare)

diurnal sleep or drowsiness. Good relief of these symptoms was reported by 15; 11 had poor results. Of these 11 patients, 5 preferred another analeptic agent. The condition of 2 was resistant to all analeptic agents, including Ritalin. Ritalin was not tolerated by 4 patients because of undesirable side effects, although 2 of these patients had a satisfactory analeptic response.

In our preliminary report, we observed that approximately half the patients with cataplexy noted elimination of, or definite decrease in, severity and number of attacks while they were taking Ritalin. In the present series, 27 patients reported on the effect of medication on their cataplexy. Excellent control was rereported by 9; 6 patients had good results; and 12 reported little or no effect. Table 1 summarizes these results.

In general, patients who observed an excellent effect on the cataplexy also reported excellent results with respect to sleepiness. However, 6 patients who reported excellent results with respect to sleepiness noted little or no effect on the cataplexy.

Episodes of sleep paralysis are not affected significantly by the use of Ritalin unless these episodes occur during the day. In such instances, elimination of drowsiness necessarily results in relief of the diurnal sleep paralysis. We have inadequate data as to the effect of Ritalin on hypnagogic hallucinations, although, in several instances, the use of hypnotic agents at bedtime has abolished hypnagogic hallucinations.

Patients who obtained a satisfactory response usually maintained the effect for the twenty-seven-month duration of the study. Of 49 patients who obtained excellent or good results, only 8 felt that the preparation had become less effective as use was prolonged. Control of cataplexy also seemed to be maintained.

Follow-up results in the original group. Of the original 25 patients previously reported on, 19 are included in this present series of 60 patients. Of the remaining 6 patients, 1 has died and 1 was treated by a colleague. A good result was obtained for the latter patient, but since the patient was not seen by one of the authors, we did not include the result in this series. We did not have adequate information about 4 patients. Of 19 original patients, 8 still reported excellent results, 5 reported good results, and 6 reported poor results. Thus, at the time of this report, 68% of the original patients regarded the effect of Ritalin as good or excellent, as compared with 84% at the time of the original study.

DOSAGE AND SCHEDULING OF DOSE

As we have emphasized previously, the physician must be flexible in scheduling the times of drug administration and should allow latitude in the total daily dosage. Most patients required 40 to 80 mg. of Ritalin daily; the median dose is 60 mg. daily. As little as 15 mg. a day was required by 1 patient, while the largest amount administered was 300 mg. a day. The condition of the patient who required 300 mg. a day was unusual, but less than this amount failed to eliminate his drowsiness. However, no other patient in the series required more than 140 mg. daily.

Since our preliminary report, we have discovered that a better stimulating effect occurs if the drug is taken thirty to forty-five minutes before meals. We have continued to caution the patient against taking the drug later than 5 P.M. until he has learned the duration of the analeptic effect.

As in most forms of therapy, in the treatment of narcolepsy better results are likely to

be obtained among intelligent patients who have a reasonable understanding of the nature of their symptoms and of the goal of therapy. On the contrary, patients of lower intelligence and patients who adopt a neurotic attitude toward their illness will be less likely to obtain the optimal response.

SIDE EFFECTS

Undesirable side effects were noted by more than half the patients who used Ritalin, although in most the effects were minor. In many instances, side effects could be eliminated by revision of the schedule or dose. Of the patients, 21 complained of slight nervousness or tremulousness; 13 had anorexia, although in only 1 was anorexia severe enough to necessitate discontinuance of use of the drug; 10 had occasional insomnia, a side effect which all patients experiencing a good analeptic effect will note if the last dose is taken too close to bedtime; 2 had palpitation and tachycardia. A patient who had a duodenal ulcer discontinued the use of Ritalin because the drug seemed to aggravate the symptoms caused by his ulcer. A papular eruption developed on the face, scalp, and chest of another patient after taking Ritalin for one month. Use of the drug was discontinued, and the eruption disappeared. Because of the excellent analeptic effect of the drug, the patient made 2 subsequent attempts to use it; these resulted in the appearance of a similar rash which again disappeared when use of the drug was discontinued. Table 2 presents the side effects in order of frequency.

SUMMARY AND CONCLUSIONS

Narcolepsy in 60 patients was treated by methyl phenidate hydrochloride (Ritalin hydrochloride) for eight to twenty-seven months. Good to excellent relief of abnormal sleepiness was reported by 49. Concurrent improvement of the cataplectic attacks occurred in 15 of 27 patients who had this symptom. Of the patients in our original report whose condition could be followed, 68% reported good to excellent results after prolonged use; the comparable figure in our earlier study was 84%. Side effects were common but were usually minor.

We still believe that Ritalin is the drug of choice in the treatment of narcolepsy. In our experience, an initially satisfactory result can be maintained after prolonged use of this agent.

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Neurologic and electroencephalographic studies in open heart surgery

A preliminary report

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IT HAS BEEN KNOWN for some time that congenital cardiac disease is often associated with other congenital abnormalities. The occurrence of brain abscess in cases of congenital shunts between the arterial and venous systems bypassing the lungs has also been known for several years.[1,2] Only in recent years, however, attention has been focused on less conspicuous neurologic abnormalities associated with heart disease.[3,4]

The recent rapid progress of cardiac surgery has underscored the problems involving the nervous system in patients with congenital heart disease. It also has emphasized the importance of studying the effects on the brain of bypass procedures in which oxygenation of the nervous system may conceivably become less than adequate.[5]

The present preliminary study is part of an investigation being carried out at the University of Minnesota Hospitals by the combined work of the Division of Neurology and the Department of Surgery. This is being done in an effort to correlate the various aspects of the problems of congenital and acquired heart disease and its treatment as reflected in the central nervous system.

MATERIAL AND METHOD

A total of 32 patients were chosen at random among 101 who were to undergo cardiac surgery with extracorporeal circulation technic during the period between July 1, 1957 and January 14, 1958. These patients were subjected to clinical, neurologic, and electroencephalographic examinations before the operation.

In addition, 2 patients admitted with tentative diagnosis indicating the probability of an open heart procedure also were studied preoperatively. Both of these patients subsequently underwent cardiac operations of "closed type," that is, without perfusion, and thus serve as controls upon the effects of thoracotomy and anesthesia. The only limiting factor in the selection was age; no children under 8 years were included. All of these patients except 8 had postoperative electroencephalograms and all except 5 had postoperative clinical neurologic examinations. Electroencephalographic records taken during the surgical procedure on 27 of the 32 patients were examined and correlated with the pre- and postoperative clinical and electroencephalographic findings.

The patients' ages ranged from 8 to 49 years. There were 3 in the first decade of life, 12 in the second, 7 in the third, 4 in the fourth, and 6 in the fifth. Clinical diagnosis of the heart condition in this group of patients was distributed as follows:

Interventricular septal defect only	6
Interatrial septal defect only	5
Mitral regurgitation (5 rheumatic, 1 fibroblastosis)	6
Aortic stenosis only (all acquired calcific)	3
Pulmonary stenosis only	1
Atrioventricularis communis	1
Tetralogy of Fallot	4
Ebstein anomaly	2
Single ventricle	1
Interatrial septal defect and pulmonary insufficiency	1

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Mitral and tricuspid regurgitation	1
Interventricular septal defect and aneurysm in sinus of Valsalva	1
Total	32
Controls	
Coarctation of aorta with aortic insufficiency	1
Mitral and tricuspid regurgitation (exploratory thoracotomy)	1
Total	2

The 2 control patients did not have electroencephalograms during surgery but otherwise were studied in the same way as those who had open heart surgery.

Electroencephalograms made during operation were graded in 6 categories, according to the amount of abnormality found, as follows:

1] No slowing below four to six per second
2] Occasional slowing below four to six per second
3] Slowing to one to three per second for short and infrequent periods
4] Slowing to one to three per second for prolonged and/or repeated periods
5] Slowing to one to three per second for prolonged and/or repeated periods and showing decreasing amplitude
6] Records showing periods of electrical silence.

Typical samples of these categories are shown in Figure 1.

Pre- and postoperative electroencephalograms were made with 8 channel machines with 20 electrodes and monopolar and bipolar technics. The "10-20" system of electrode placement was used in all the cases. Electroencephalograms during surgery were made with a 2-channel machine and 4 electrodes, 2 over each hemisphere.

In the evaluation of the pre- and postoperative electroencephalograms, the usual criteria for abnormality were employed. In the children between 8 and 14 years of age who are included in this report, the abnormalities consisted of spikes, high-voltage sharp waves, and delta activity at high voltage or in large amounts. Theta was considered abnormal in 14-year-old patients when it [1] showed high voltage or [2] constituted more than 20% of the activity of parietal, posterior temporal, and occipital areas. It was also considered abnormal when it had paroxysmal characteristics, even in younger patients, as was the case in a 10-year-old child. Theta activity was considered abnormal in adults below 25 years of age when it constituted more than 10% of the occipital, parietal, and posterior temporal frequencies, when it was paroxysmal, or when it showed higher voltage than the background activity. Any amount of theta activity exceeding 5% of the activity in any area of the head was considered abnormal in patients over 25 years of age. Obviously, these percentages are

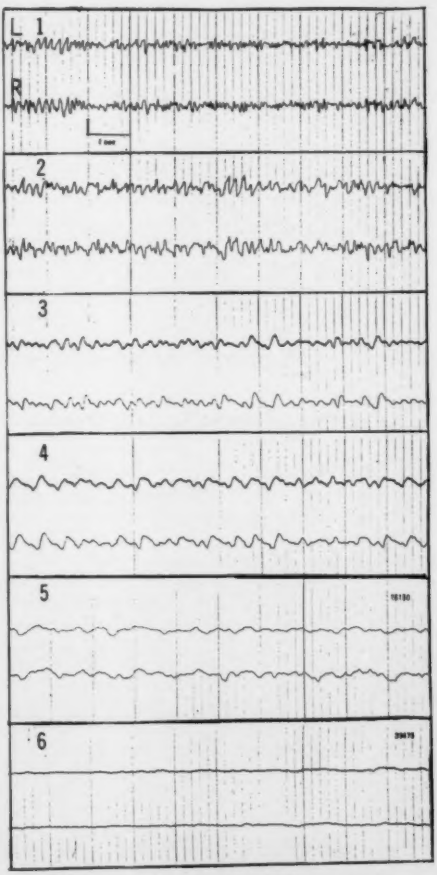

Fig. 1. Samples of surgical electroencephalograms typical for each of six categories of abnormality. Upper channel, left hemisphere; lower channel, right hemisphere. Voltage calibration = 100 μV.

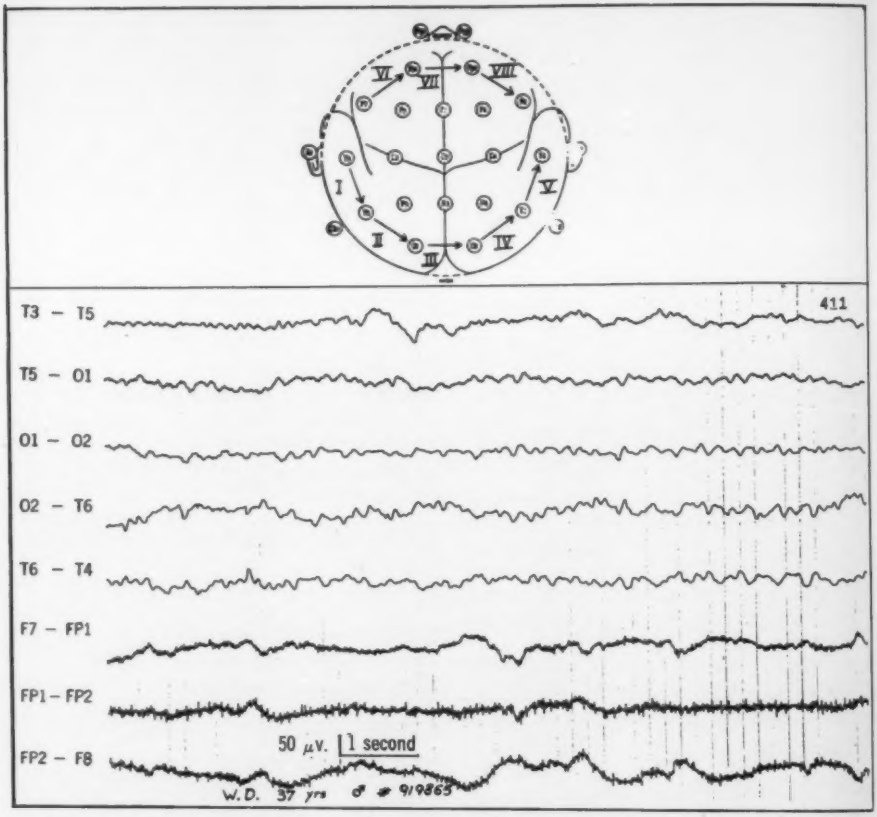

Fig. 2. Record showing predominant abnormality (slow activity) in posterior temporal and occipital areas. Resting record

only approximate and are used here in order to give a general idea of our criteria for evaluation.

RESULTS

Of the 32 patients, 11 (34%) had abnormal electroencephalograms before the operation. This abnormality was mild to marked. Tracings showing only minimal abnormality are not included in these 11.

The abnormality was diffuse in 9 cases and focal in 2. Of the 11 abnormal records, 8 (73%) showed a clear predominance of the abnormality in the posterior cerebral regions (parietal, posterior temporal, and occipital, Fig. 2). One of these showed a slow dominant frequency (7 per second) appearing in central, parietal occipital, and posterior temporal areas. This activity blocked with vision. There were 3 records which showed paroxysmal features (Fig. 3). Rhythmic sharp waves were seen in 1 case and isolated spikes in 3 cases (Table 1).

Of the 32 patients undergoing open heart operations, 24 had electroencephalograms taken after surgery. Of these, 15 had records within ten days after the operation, 5 had their records within two weeks after the operation, and the rest had theirs on the twentieth, twenty-first, twenty-second, and twenty-fifth postoperative days. The time elapsed between the operation and the first postoperative electro-

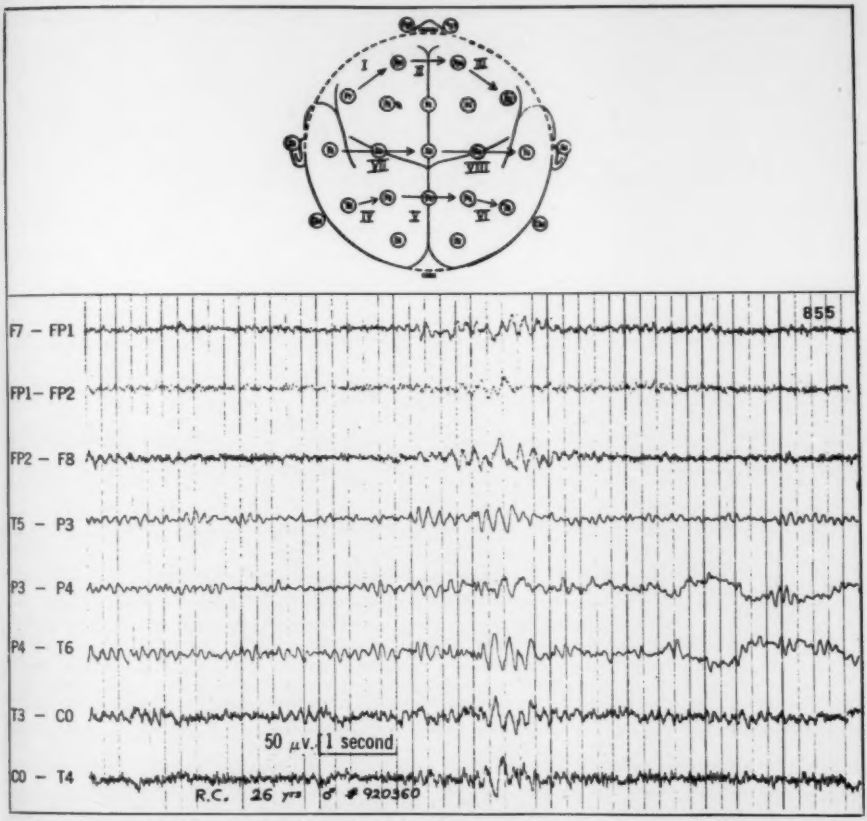

Fig. 3. Generalized bursts of moderately high voltage 5 and 6 per second waves. Resting record

encephalogram had, generally speaking, a direct relation to the condition of the patient after surgery; satisfactory records could not be obtained until chest tubes had been removed and the patient was free of discomfort and able to be moved to the testing laboratory. This was very difficult during the first few postoperative days and it can be said that, in general, the better the patient's general condition, the sooner his cooperation for a satisfactory record was secured.

In several patients with complete heart block being maintained upon the myocardial electrode and electrical pacemaker, testing was necessarily delayed until sinus rhythm had returned and they could be moved.

Of these 24 first postoperative records, 16 showed more marked abnormality than before operation, 5 were essentially unchanged, and 3 showed improvement.

Both of the control patients, who had uncomplicated cardiac operations without perfusion (resection of coarctation of aorta and exploratory thoracotomy only) had postoperative electroencephalograms showing more marked abnormality than before surgery.

Of the 16 patients who had first postoperative records showing more abnormality than the preoperative electroencephalograms, 10 had a second postoperative tracing within ten days after the first. In 6 patients, the record had reverted at that time to the preoperative level (Fig. 4). Of the other 4, 2 had reverted to preoperative type of record in eleven

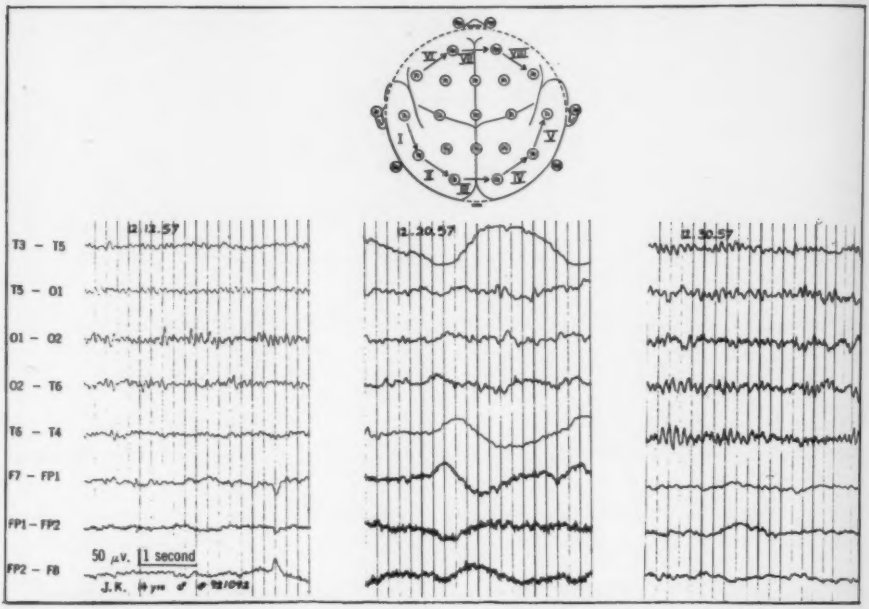

Fig. 4. Samples of preoperative record and first and second postoperative records. The first tracing only shows mild abnormality consisting of sharp and theta activities in the posterior leads. First postoperative record shows large amount of theta and delta activities. High voltage very slow baseline shift is due to perspiration. Second postoperative record is similar to preoperative tracing. This patient had open heart surgery for correction of interventricular septal defect on December 13, 1957.

and twenty-four days respectively after their first postoperative tracing (twenty-three and forty-eight days, respectively, after the operation). One was discharged from the hospital without a third postoperative record. His second postoperative electroencephalogram, however, although still more abnormal than before surgery, showed improvement over the first postsurgical tracing. The remaining patient still showed a more marked abnormality than in the preoperative record in tracings taken seventeen and forty-eight days after surgery. The abnormality showed fluctuations, but the last record was the most abnormal.

Clinical diagnosis of the 3 patients who showed improvement in their electroencephalograms shortly after surgery, as compared with their preoperative tracings, was interventricular septal defect in 2 and mitral regurgitation in 1. Of these, 2 had a second postoperative record. One reverted to a mild preoperative abnormality, and the second showed still only a moderate abnormality, as compared with marked diffuse abnormality preoperatively, twenty-seven days after the operation. Table 2 summarizes the results of postoperative electroencephalograms.

Electroencephalographic tracings taken during the operation were classified according to our 6-group system and correlated with preoperative and first postoperative electroencephalograms (Table 3).

Most of the records made during surgery were classified as grade 3. There were 15 out of the 27 surgical tracings (55.5%) in grades 1 to 3 and 12 records (44.5%) in grades 4 to 6. In the first group, there were 5 patients with abnormal preoperative and 9 with abnormal postoperative records; 1 patient died before a postoperative tracing could be obtained. The second group of patients, with surgical tracings in grades 4 to 6, had 3 abnormal pre-

operative and 6 abnormal postoperative tracings. In this group, 5 patients died postoperatively and no record could be obtained after the operation (Table 4).

Of the 32 patients interrogated and examined clinically before the operation, 9 (28%) had definitely positive neurologic past histories. This included sudden hemiplegia, convulsions, episodes of diplopia or blindness, and chorea. History referring to ocular symptoms was fairly common; 3 patients had suffered transient episodes of diplopia, and 1 had no episode of transient unilateral blindness.

Only questionable abnormal neurologic features were found in the histories of 5 patients. The rest (18) had no positive histories.

Of the 32 patients examined preoperatively, 11 (34%) were found to have definite abnormal findings in the neurologic examination. Only 2 of these had a positive neurologic history. Of these 11, abnormal preoperative electroencephalograms were noted in 6 (54.5%). Postoperatively, 5 died. The total number of dead in the group of 32 was 9. Therefore, 55% of the deaths occurred in patients who had abnormal neurologic findings before surgery. This correlation was not surprising in view of the far-advanced and even terminal condition

TABLE 1
PREOPERATIVE ELECTROENCEPHALOGRAPHIC ABNORMALITIES

Case	*Age and sex*	*Degree of abnormality*	*Type of abnormality*	*Diffuse (predominant areas)*	*Focal (area)*	*Clinical diagnosis*
P.K.	14 M	Mild	Rhythmic sharp waves	Central and parietal bilaterally		Interatrial septal defect
R.S.	14 M	Moderate	Slow waves (delta and theta) and spikes, paroxysmal	Occipital, posterior temporal areas		Ebstein complex
M.R.	10 F	Marked	Slow waves (theta) and spike	Occipital, posterior temporal areas		Interventricular septal defect
M.O.	14 F	Moderate	Slow waves (theta) and sharp waves	Central and temporal areas	Sharp waves right central and parietal	Interatrial septal defect; pulmonary hypertension; infarction left upper lobe
L.T.	10 F	Moderate	Slow waves (theta) paroxysmal	Left parietal, posterior temporal		Interventricular septal defect
W.D.	37 M	Moderate	Slow waves (theta), sharp waves	Central, parietal, and posterior temporal	Theta, posterior temporal, parietal	Mitral regurgitation
D.S.	29 F	Mild	Slow waves (theta)	Posterior temporal, occipital		Interventricular septal defect and aneurysm in sinus of Valsalva
R.C.	26 M	Mild	Slow waves (theta)	Central, parietal, occipital posterior, temporal		Interatrial septal defect
D.C.	39 F	Moderate	Slow waves (theta) and paroxysmal	All areas		Mitral regurgitation
J.K.	14 M	Mild	Slow waves (theta), sharp waves and spikes	Right occipital and parietal areas		Interventricular septal defect
M.C.	14 M	Mild	Slow waves (theta), sharp waves	Posterior temporal		Pulmonary stenosis

TABLE 2
POSTOPERATIVE ELECTROENCEPHALOGRAMS

	Immediate	*Final*	*No follow-up*
More abnormal than before surgery	16 (67%)	2	6
Less abnormal than before surgery	3 (12%)	1	1
Unchanged	5 (20%)	14	

TABLE 3

Grade of abnormality in electroencephalograms during surgery	*Number of cases*	*Number of abnormal preoperative electroencephalograms*	*Number of abnormal first postoperative electroencephalograms*	*Remarks*
1	4	1	1	One patient died postoperatively. No postoperative electroencephalogram
2	4	1	3	
3	7	3	5	
4	5	2	3	One patient died postoperatively. No postoperative electroencephalogram
5	4	0	2	Two patients died postoperatively. No postoperative electroencephalogram
6	3	1	1	Two patients died postoperatively. No postoperative electroencephalogram

TABLE 4

		Number of abnormal preoperative tracings	*Number of abnormal first postoperative tracings*	*Postoperative deaths*
Surgical tracings in groups 1 to 3	15 (55%)	5 (33% of 15)	9 (60% of 15)	1 (6.6% of 15)
Surgical tracings in groups 4 to 6	12 (45%)	3 (25% of 12)	6 (50% of 12)	5 (41.6% of 12)
Totals	27	8	15	6

of a number of the patients in this group. Moreover, it should be pointed out that several patients had conditions (mitral regurgitation, Ebstein's malformation) for which surgical treatment was at the time in a developmental status.[6,7] Table 5 summarizes in greater detail these patients with abnormal neurologic findings, with their age, sex, clinical diagnosis of their cardiac condition, and type of preoperative electroencephalogram.

Of the patients who expired postoperatively, 4 could be examined after surgery before they died; 3 had abnormal neurologic findings. Of the surviving 23 patients, 9 (39%) showed abnormal neurologic findings after surgery. Of these, 5 had abnormal neurologic examination before surgery and 4 showed abnormalities only after operation. Of the latter group, 1 patient had returned to normality seven days after the operation. None of the patients showing abnormalities before surgery had a normal neurologic examination after surgery.

As mentioned above, of the 11 patients who had abnormal preoperative neurologic findings, 6 (54%) also had an abnormal preoperative electroencephalogram. Of the 9 patients who had abnormal findings in the postoperative neurologic examination and who had postoperative electroencephalograms, 7 (78%) had abnormal electrical patterns.

No significant correlation was found between electrical or neurologic abnormalities and the following factors:

1] Constant or intermittent cyanosis
2] Blood pressure during surgery
3] Oxygen saturation measured during the surgical procedure
4] Duration of extracorporeal circulation (thirteen to seventy-nine minutes in our series).

DISCUSSION

The incidence of abnormal neurologic findings in the preoperative examinations of our

patients is higher than that reported by other workers. Tyler and Clark[3] in a much larger series than ours investigated the incidence of neurologic complications in congenital heart disease and found that 25.4% of their patients presented these complications. Shev and Robinson[8] report an incidence of 28.5% recognizable neurologic disorders in their series of 28 patients. Comparison with the series of Tyler and Clark makes us think that the higher incidence of neurologic abnormalities in our group is probably partly due to the fact that we included all the positive neurologic findings, even when there was no history of neurologic disease and in many cases no complaints referring to the central nervous system. As our study is oriented toward a detailed investigation of alterations of the nervous system that are present concomitantly with heart disease, we thought it would be in accordance with this objective to include any neurologic finding that is generally considered to be outside the limits of normal variation. Shev and Robinson do not give details about their neurologic findings as their study was primarily oriented toward electroencephalographic abnormalities. Tyler and Clark do not include isolated abnormal neurologic findings in their report, and they deal only with conditions producing symptoms referable to the nervous system. A second source of discrepancy between the incidence of neurologic abnormalities in our series and those mentioned above may be the difference in age groups. Shev and Robinson dealt with patients ranging in age from 4 days to 18 years. Tyler and Clark do not specify the age range of their material, but we may safely infer that their oldest patient was 15 years old or less, as their material was extracted from a cardiac clinic of a pediatric

TABLE 5
PATIENTS WITH ABNORMAL PREOPERATIVE NEUROLOGIC FINDINGS

Case	*Age and sex*	*Clinical diagnosis*	*Preoperative clinical examination*	*Preoperative electroencephalogram*	*Remarks*
S.D.	17 M	Interventricular septal defect; infundibular stenosis; pulmonary valve stenosis; cardiac insufficiency; cyanosis	Anisocoria, right central facial paresis, right Babinski	Normal	Died
M.H.	27 F	Interatrial septal defect	Babinski and Hoffman on the left	Normal	
N.B.	19 F	Mitral insufficiency; rheumatic congestive failure A.H.A. class IV	Left twelfth nerve weakness, choreic posture of hands	Normal	
W.N.	47 M	Aortic stenosis, calcific in congestive failure A.H.A. class IV	Ataxic tremor in left hand, left hyperreflexia	Normal	Died 48 hours postoperative. Postmortem: diffuse cardiac necrosis
R.S.	14 M	Ebstein anomaly, cyanotic in congestive failure A.H.A. class IV	Low intelligence, right hyperreflexia, questionable left Babinski	Abnormal	Died; cardiac insufficiency
M.O.	14 F	Interatrial septal defect, pulmonary insufficiency	Retarded physical development, excentric pupils	Abnormal	Died
L.T.	10	Interventricular septal defect	Macrocephaly, weakness of right lower extremity	Abnormal	
W.D.	37 M	Mitral regurgitation; rheumatic in congestive failure A.H.A. class IV	Left exophoria, reflex asymmetry	Abnormal	Died postoperatively of coronary thrombosis
R.C.	25 M	Interatrial septal defect	Left hyperreflexia, left Babinksi	Abnormal	
J.K.	14 M	Interventricular septal defect with severe pulmonary hypertension	Right hyperreflexia, questionable right Babinski	Abnormal	
E.M.	9 F	Interventricular septal defect	Left internal rectus palsy, questionable left Babinski	Normal	

service. Our youngest patient, on the other hand, was 8 years old, and, of the 32 patients included in our series, only 11 were under 18 years of age.

In favor of the age factor as cause of discrepancy are the pathologic abnormalities present in the central nervous system in association with congenital heart disease. Cohen and Baker[4] reported pathologic changes which included encephalomalacia from anoxic episodes, diffuse gliosis, focal demyelination and calcification, symmetric pontine demyelination in the region of reticular formation, and telangiectasis. It is well known that vascular malformations in the central nervous system very often give symptoms or signs only in adult life. Focal demyelinated areas may also be silent in the early ages of life and only become manifest by the appearance of abnormal function in the course of normal development.

The incidence of abnormal electroencephalograms was significantly higher in the series of Shev and Robinson than in ours. A possible partial explanation, which cannot be verified from the available data, may be found in the fact that in their group some patients had more than one tracing and the percentage of abnormality was calculated for the total number of records. There may also be a difference in criteria for abnormality, and another likely cause for the different results is the small number of cases in both the series of Shev and Robinson and in our series. This, of course, also has to be kept in mind for the difference in percentages of clinical neurologic abnormalities between our sample and the two other samples analyzed above. Only the report by Tyler and Clark comprises a sufficient number of cases.

The occurrence of electroencephalographic abnormality in the posterior area of the head in a considerable number of cases in our series and the fact that it was limited to these areas in many of them seems quite significant. It has been found that children, in general, present a larger number of abnormalities in the occipital leads of their electroencephalograms.[9] Of the 8 patients who showed predominant abnormality in the posterior part of the brain in our group, 5 were between 10 and 14 years of age and the other 3 were 20, 26, and 37 years old. Although the groups are too small to draw any conclusions from, we would like to suggest that the older patients and also possibly patients 14 years old show an electrical abnormality which may indicate a persistence of immature electroencephalographic features for their age and that this may be somehow related to congenital abnormalities associated with their heart disease. This idea is supported to some extent by the pathologic abnormalities reported in the central nervous system by Cohen and Baker in cases of congenital heart disease.[4] Focal areas of demyelination and calcification may interfere with maturation of electrical rhythms. With the possible exception of 1 who may have had an acquired defect, our 8 patients showing preoperative electroencephalographic abnormalities predominant in posterior areas of the brain all suffered from congenital heart disease. This, however, may be misleading due to the fact that a great majority of our whole group of patients had disease of congenital origin. At any rate, this area of our study seems to be promising for the investigation of genesis and development of electrical activity of the human brain.

Analysis of neurologic and electroencephalographic findings in relation to open heart surgery gives interesting although preliminary and only suggestive data. The postoperative mortality that was found in this group is by no means a representation of the mortality in the large number of operations with extracorporeal circulation that have been performed at this hospital. From this point of view, ours is definitely a selected sample with disproportionately high percentage of poorer risk patients. Thus, the figure of 26.8% mortality in our group of 32 cannot be considered representative.

The reasons for this degree of selection are clear. In this preliminary survey study, facilities were adequate to permit testing of only one-third of the patients selected for intracardiac surgery. The poorest risk patients were nearly always hospitalized for a number of days before operative treatment, and thus a high proportion of these patients could be tested and examined preoperatively. This is further supported by the number of patients with acquired diseases of the aortic or mitral valves and by the inclusion in our series of 2 patients with the relatively rare Ebstein malformation, both of which were admitted in

terminal condition. In contrast, patients with uncomplicated problems to have elective corrective procedures often were admitted and operated upon before the studies could be carried out. For the same reasons, any suggestive correlation between degree of abnormality of surgical tracing and number of postoperative deaths has to be further evaluated.

Correlation of incidence of abnormal postoperative electroencephalograms with degree of abnormality in the surgical tracings is not significant.

It is interesting to note that increased abnormality in postoperative electroencephalograms as compared with the preoperative tracings were only transitory in almost all cases. Permanent improvement of the preoperative electrical pattern after surgery, on the other hand, was very rare and was seen in only 1 or 2 patients. It is to be expected that damage to the central nervous system caused by a congenital anomaly will not be reversible, especially when the patient has reached adult life. It would be surprising, therefore, to find improvement of electrical activity or of neurologic findings in an adult, even after the primary defect in the heart has been corrected.

The necessity of controls who have been submitted to anesthesia and surgical operations not involving extracorporeal circulation was pointed out by the findings in the 2 patients included as controls in this series, who underwent intrathoracic surgery without extracorporeal circulation. Both had postoperative electroencephalograms which were definitely more abnormal than the preoperative tracings. This finding warrants considerably more study since both patients had entirely uncomplicated procedures. The increased abnormality was only transitory, and the records reverted to preoperative levels in two to three weeks.

SUMMARY

Neurologic and electroencephalographic examinations were made in 32 patients before open heart surgery and in most of them after surgery; 27 had electroencephalographic records made during the surgical procedure.

Results of these examinations revealed a high percentage of abnormal electroencephalograms and neurologic examinations before surgical treatment in patients with heart disease (34%).

In most of the patients who showed electrical abnormality (73%), this was predominant in posterior temporal, parietal, and occipital regions.

The surgical procedure in most cases only temporarily affected the electroencephalographic record and the clinical neurologic picture. In 2 control patients having anesthesia and uncomplicated intrathoracic operations without perfusion, postoperative electroencephalograms were temporarily more abnormal than their preoperative tracings.

It is suggested that congenital alteration of cerebral blood supply secondary to heart disease produces disturbances which prevent the normal maturation of electrical rhythms. This is manifested in adults by electroencephalographic abnormalities that resemble those frequently seen in children.

Future correlation of neurologic and electroencephalographic findings with pathologic studies of the central nervous system will probably greatly contribute to the study of origin and development of cerebral electrical activity.

ACKNOWLEDGMENT

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Lipid content and phospholipid synthesis in degenerating sciatic nerve of dogs

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AFTER SECTIONING of a peripheral nerve, typical histologic changes, termed wallerian degeneration, are observed. As this seems to be primarily an atrophy, a decrease of all lipid fractions would be suspected. The literature[1–5] includes reports of a decrease in neutral fat, total lipids, phospholipid phosphorus, acid soluble phosphorus, total cholesterol, and cerebrosides in the degenerating portion of sciatic nerves of cats and rats. In monkeys, a greater uptake of P^{32} in all lipid fractions in regenerating and degenerating peripheral nerves is reported.[6] Magee and Rossiter[7] demonstrated increased specific activity of lipid phosphorus in degenerating cat sciatic nerve in an in vitro study.

In view of these observations, experiments were undertaken to compare the lipid content and phospholipid synthesis in degenerating sciatic nerve with the intact nerve in the opposite leg of the same dog. To our knowledge, there have been no studies in this species. Likewise, the relative specific activity of the phospholipid turnover has not been previously determined.

METHODS

The sciatic nerves of 13 male and 1 female mongrel dogs, weighing 7.5 to 27 kg., were cut in one leg, the opposite nerve serving as a control. An intramuscular injection of 300 μc. of P^{32} was given seven and one-half* hours before the animals were sacrificed by exsanguination one, two, four, five, six, seven, eight, ten, thirteen, twenty-one, twenty-seven, thirty-three, and thirty-six days after nerve sectioning. The sciatic nerves distal to the point of sectioning were then removed from the denervated and normal limbs. Tissues were weighed and acid-soluble phosphorus removed by extraction with 10% trichloroacetic acid (TCA) containing 0.4% magnesium chloride.[10] Total radioactivity[11] and phosphorus content[12] of the acid soluble extract were determined, and TCA residues were extracted with alcohol for eight hours in a continuous Soxhlet extractor to remove lipids which were then purified in chloroform.[11] Total lipids, phospholipid phosphorus,[1] radioactivity,[10] and cholesterol[13] were determined on aliquots of the chloroform solution.

As a measurement of phospholipid turnover, relative specific activities were calculated. This is the ratio of specific activities of phospholipid phosphorus to specific activities of inorganic phosphorus. Under conditions of our experiment, an increase in formation of phospholipids may reasonably be assumed when higher values of relative specific activities are found.[14,15]

RESULTS

Data obtained from the present investigation are reported in Table 1, and each cut nerve has been compared with its own control. The mean values and standard deviations derived from the nerves of 14 control animals of the relative specific activity of phospholipids, total lipids, phospholipid phosphorus, and cholesterol were 8 ± 3, 13.14 ± 2.97, 133 ± 25, and 1520 ± 206, respectively. Phospholipid

*This time interval corresponds to the ascending part of the specific activity time curves, where synthesis of phospholipid in the dog occurs to a degree greater than breakdown.[9] Chaikoff and Zilversmit[9] have shown there is a progressive uptake of P^{32} into the phospholipids of muscle, liver, and kidney of the dog from six to eighteen hours after administration of the isotope.

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TABLE 1
EFFECT OF NERVE SECTION ON LIPID CONTENT AND PHOSPHOLIPID SYNTHESIS IN SCIATIC NERVE OF DOG

Time of Degeneration	Degenerating Nerve			
	Phospholipid Phosphorus	Total Lipids	Phospholipid Phosphorus	Cholesterol
(days)	(RSA* × 1,000)	(gm. per 100 gm. wet tissue)	(mg. per 100 gm. wet tissue)	(mg. per 100 gm. wet tissue)
1	19 (.58)†	14.43 (.70)	121 (.88)	1550 (.83)
2	25 (.32)	13.75 (.73)	68 (1.68)	773 (1.76)
4	10 (1.2)	12.99 (1.11)	108 (1.24)	1276 (1.23)
5	20 (.40)	7.33 (1.52)	104 (1.41)	1049 (1.43)
6	32 (.31)	9.21 (1.28)	72 (2.29)	816 (2.21)
7	14 (.25)	7.93 (1.30)	84 (1.61)	981 (1.45)
8	17 (.41)	8.61 (1.28)	77 (1.51)	891 (1.47)
10	15 (.33)	15.40 (1.30)	91 (1.60)	1381 (1.20)
13	27 (.55)	9.93 (1.58)	60 (2.48)	836 (2.06)
21	20 (.30)	20.09 (.70)	93 (1.54)	1019 (1.72)
27	7 (.86)	12.96 (1.23)	93 (1.96)	1121 (1.65)
30	19 (.36)	11.19 (1.39)	55 (2.05)	688 (1.80)
33	17 (.65)	11.44 (1.45)	86 (1.38)	1056 (1.26)
36	17 (.29)	7.64 (1.28)	35 (2.51)	1276 (1.15)

* RSA = relative specific activity
† The figures in parenthesis are the ratio of values of control/degenerating nerve.

phosphorus and total cholesterol content were found to be lower in the cut nerve than in the control. The phospholipid phosphorus and cholesterol content decreased on the second day after section; however, the total lipids concentration did not decrease until the fourth day. This decreased concentration of lipids after nerve injury is similar to the findings of Mannell[3] in rats and Johnson and associates[1] and Burt and associates[2] in cats. Relative specific activity values of phospholipids were found to be higher in cut nerve throughout all stages of degeneration. This observation agrees with Bodian and Dziewiatkowski's[6] study in monkeys and Magee and Rossiter's[7] investigation in cats. It is interesting to note that the turnover rate of phospholipids is increased during degeneration despite the fact that the lipid phosphorus content is decreasing. Rossiter and associates[16] have stated that such findings suggest an increase in the potentiality of the nerve for remyelination.

SUMMARY

1] Total lipids, phospholipid phosphorus, total cholesterol, and radioactivity were determined in cut sections of sciatic nerves of dogs.

2] Total lipids, phospholipid phosphorus, and total cholesterol were found to be decreased in cut sections of sciatic nerves of dogs during a period from two to thirty-six days after sectioning.

3] Phospholipid turnover increased in cut nerves in a period from one to thirty-six days after injury.

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Effects of Diamox on epileptic monkeys

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IT IS WIDELY recognized that epileptic seizures may be precipitated in the human being by manipulation of dura adherent to underlying cortex. That seizures occur during the surgeon's efforts to remove the dura from the cortical scar might lead one to believe that mechanical stretching of dendrites in the cortex may be responsible for precipitation of the fit.

Microelectrode studies of the activity of single neurons in the epileptogenic focus indicate that the characteristic of autonomous discharge, often in prolonged high frequency bursts, distinguishes an epileptic unit from the behavior of a normal cell.[10]

It has been postulated that such autonomous activity may be due to a difference in potential between the cell body and its dendrites.[11] This difference could be due to a relatively enduring dendritic depolarization. Under these circumstances, the membrane potential of the soma of the neuron recovers rapidly, acting as a source, with resulting current flow from the soma to the depolarized dendritic tree which acts as a sink. If this current flow reaches threshold for the soma, an autonomous discharge will occur.

The underlying causes of this potential difference between the soma and its dendrites have been postulated to be secondary to pathologic changes in the dendrites in which mechanical deformation by the scar tissue could play a part.[11] Stretching of the dendrites in certain sensory receptors results in their depolarization;[3] possibly, this is a general property which is potentially shared by all dendrites in the central nervous system.[4]

In order to test the hypothesis that stretching of cortical dendrites may influence the activity at the cortical epileptogenic focus, the effect of intravenously administered Diamox (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) in epileptic monkeys was studied.

Previous studies by Knopp, Atkinson, and Ward[5] indicate that intravenous Diamox rapidly increased cerebrospinal fluid pressure in cats and monkeys; the pressure returned to normal levels within an hour. Diamox produces a bimodal increase in cerebrospinal fluid pressure, 1 peak occurring one minute after administration and 1 occurring eight to ten minutes after administration.

Subsequent studies utilizing radioactive tracer technics[1] indicate that the initial increase in cerebrospinal fluid pressure one minute following administration of Diamox reflects an increase in arterial and venous pressure and an increase in intracranial blood volume. The second cerebrospinal fluid pressure peak occurring eight to ten minutes following administration of Diamox is, however, associated with falling arterial and venous pressure and an intracranial blood volume near the control level; this peak is thus not the direct result of increased intracranial blood volume.

Since the volume of erythrocytes—which are laden with carbon anhydrase—increases after Diamox administration, Atkinson and Ward[1] postulated that this second rise in cerebrospinal fluid pressure might be secondary to similarly increased fluid uptake by brain tissue because of a rise in intracellular, osmotically active carbon dioxide. If such an increase of brain volume occurs, it might possibly increase the degree of dendritic stretch in the epileptogenic focus with augmented spike activity in the electroencephalogram and even precipitation of seizures. These experiments were carried out to investigate this possibility.

METHODS

Epilepsy was induced in 8 monkeys (Macaca mulatta) by the sterile injection of alumina cream into the sensorimotor cortex. The

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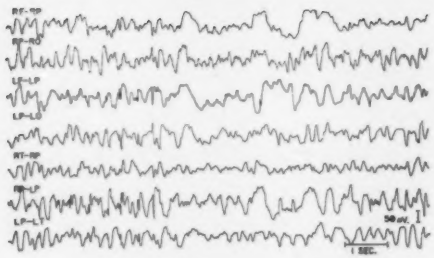
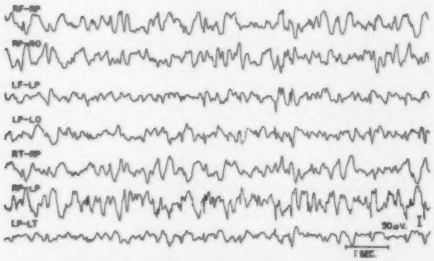
Figure 1



Control electroencephalogram. An epileptic monkey with focal spikes in the left sensorimotor cortex; generalized electroencephalographic abnormalities



No dramatic change in epileptic activity is seen four and one-half minutes after intravenous administration of 100 mg. per kilogram of Diamox

current experiments were carried out one and one-half to two years after operation in 4 adult animals and six to eight weeks after operation in the remaining 4 monkeys. At the time of these experiments, motor seizure activity had been observed in 5 of the animals.

In each experiment, the unanesthetized monkey was placed in a restraint box and the scalp electroencephalogram recorded by needle electrodes and an 8-channel Grass electroencephalograph. After an adequate control electroencephalogram had been recorded for ten to fifteen minutes, 150 mg. per kilogram of Diamox was injected intravenously. Continuous electroencephalographic recording was obtained during the injection and for forty-five to sixty minutes thereafter; the cerebrospinal fluid pressure changes induced by Diamox had been shown to fall within this period.

RESULTS

In none of 8 monkeys was any definite alteration of the spike activity observed which could be attributed to the intravenous injection of 150 mg. per kilogram of Diamox. If spike activity was not present in the control electroencephalogram, none was ever induced by Diamox. Opposite extremes are presented of spontaneous electroencephalogram activity found in this series of 8 epileptic monkeys.

In Figure 1, the control electroencephalogram shows diffuse abnormalities with multiple spikes with a recorded phase reversal over the epileptogenic focus in the left sensorimotor cortex. This monkey had been observed to have spontaneous seizures. After the intravenous injection of Diamox, no dramatic change occurred in the frequency or amplitude of the spike activity, although the entire record appeared somewhat slowed. Possibly, drowsiness was induced in some animals.

In contrast, the control electroencephalogram of the monkey illustrated in Figure 2 does not exhibit any large spikes although, at other times, occasional low-amplitude sharp-wave activity was recorded from the region of the epileptogenic focus. After intravenous Diamox, no spike activity was induced and the record was again somewhat slowed.

DISCUSSION

These experiments would seem to indicate clearly that Diamox, in doses known to increase brain volume, neither induces clinical seizure nor increases the spike activity in the electroencephalograms of epileptic monkeys. These results were not entirely unexpected since clinical studies have indicated[6,7] that Diamox may have an anticonvulsant action. Experimental studies have shown that the threshold of induced electroshock seizures is closely correlated with the level of carbonic anhydrase activity in the developing brain of young animals.[8]

Millichap, Woodbury, and Goodman[9] have further shown that Diamox produces a rise in the electroshock threshold in mice. Their preliminary experiments indicated that the drug caused a decrease in total brain sodium and an increase in the ratio of intracellular to extracellular potassium concentration in brain. They further postulated that, since an increase

in the ratio of extracellular to intracellular brain sodium concentration probably increases the membrane potential, a large reduction in excitability might be produced in long neuronal chains which may well be involved in the spread of convulsive phenomena. Possibly, this anticonvulsant activity of Diamox overshadows any increase in epileptic activity secondary to dendritic stretch induced by the increase in brain volume produced by Diamox.

However, a second possible explanation exists. Davenport[2] has demonstrated that electrical after-discharge evoked by local stimulation of the cortex is independent of carbonic anhydrase. This would be consistent with the observation of Millichap[8] that minor convulsive activity in the newborn rat is resistant to Diamox. If it is true that local neuronal events in the cortex (in contrast to long-chain reverberating circuits) are not significantly altered by Diamox, any increase of local epileptogenic activity in our epileptic monkeys would not be masked. Thus, the increase in brain volume produced by Diamox, if it produced dendritic stretch resulting in increased dendritic depolarization, should have been manifested by an increase in epileptic activity in the electroencephalogram. This was not seen.

In view of these contrasting possible explanations of our results, clearly these experiments do not illuminate the hypothesis that stretching of cortical dendrites may influence the activity at a cortical epileptogenic focus.

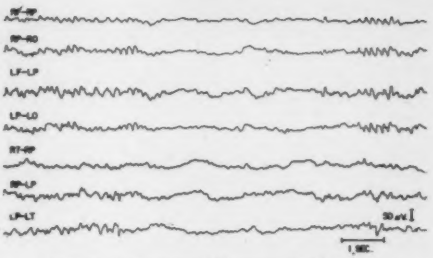
SUMMARY

1] It has been postulated that stretching of cortical dendrites may influence the activity at a cortical epileptogenic focus. Since Diamox increases brain volume, dendritic stretching at the cortical scar might result.

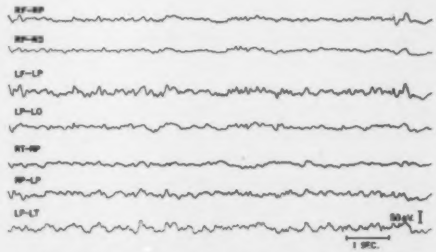
2] Epilepsy was induced in 8 monkeys by the alumina cream method. Continuous electroencephalographic recording was carried out during and after the intravenous administration of Diamox.

3] No significant alteration of the electroencephalogram was seen in any of these animals. The possible mechanisms participating in this phenomenon are discussed.

Figure 2



Control electroencephalogram. Epileptogenic focus left sensorimotor cortex with only slight electroencephalographic abnormalities



No spike activity induced two and one-half minutes after intravenous administration of 100 mg. per kilogram of Diamox

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Relation of periaqueductal gray matter to stomach and bladder motility

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THE PERIAQUEDUCTAL gray matter is related to the hypothalamus. The dorsal longitudinal fasciculus of Schütz, containing fibers that probably arise throughout the hypothalamus—especially in its posterior part—travels through this region.[1–6]

Marburg[7] stated that the fibers of this system are related to the nuclei of the periaqueductal gray matter. Bucher and Bürgi[8] described 3 fiber systems associated with the periaqueductal gray matter, 2 of which established connections with the hypothalamus—a fasciculus perifornicalis rising from the gray matter and going to the perifornical region and another system of fibers traceable to the ventromediocaudal parts of the massa intermedia and to the posterior hypothalamus. Conversely, Bucher and Bürgi also demonstrated that lesions in the posterior hypothalamus caused degeneration of similar, but descending, fibers which appeared to distribute to the periaqueductal gray matter at various levels, sometimes as far back as the midbrain isthmus.

Investigations were undertaken in an effort to determine whether or not functional, descending, autonomic pathways could be delineated within the periaqueductal gray matter. The results of 2 of these investigations are presented—those dealing with the effect of stimulation and ablation of the gray matter on stomach and bladder motility. The influence of the central nervous system on bladder and gastrointestinal functions has been investigated for some time. Only those articles which appeared pertinent to the present experimental work are presented.

In 1932, Beattie,[9] using the direct approach, demonstrated increased gastric peristalsis resulting from stimulation of the walls of the third ventricle in the region of the lateral margins of the infundibulum. Later, Beattie and Sheehan,[10] again using a direct approach, demonstrated increased peristalsis and tonus from stimulation in the region of the tuber and a slight decrease in tone and cessation of peristalsis from stimulation in the posterior hypothalamic region. Both papers reported that vagal section abolished the increased activity. Kabat and associates[11] demonstrated that stimulation of the lateral hypothalamic region caused cessation of peristalsis and loss of tone. They placed electrodes under stereotaxic control in unanesthetized cats and made roentgenograms of the stomach. Stimulation of other points in the hypothalamus, preoptic region, and other diencephalic structures yielded no response, and at no time was excitation elicited. Heslop[12] confirmed Beattie and Sheehan's apparent localization of an anterior excitatory region and a posterior inhibitory region in the hypothalamus. Wang and associates[13] reported that anterior hypothalamic stimulation usually gave increased peristalsis and tonus after a latent period of forty to sixty seconds. If the gut was quite active, an initial inhibition might occur which would be followed by increased tension and activity. Bilateral vagotomy did not abolish these responses. They found that stimulation at the level of the infundibulum and mammillary bodies gave rise to an immediate increase in tension and activity. These responses were abolished by vagotomy. In 4 cats, the delayed response was stopped by acute cord transection at the upper thoracic level.

Sheehan[14] was able to elicit inhibition from stimulation of the lateral and posterior hypothalamic regions along with other sympathetic

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responses, such as pupillary dilation, widening of the palpebral fissures, and piloerection. On occasion, Sheehan elicited excitation from the preoptic and supraoptic regions. However, excitation was obtained with less regularity than inhibitory responses.

Eliasson[15] in 1954 reported an extensive study on gastrointestinal activity resulting from brain stem stimulation in the cat. The thalamus, hypothalamus, mesencephalon, pons, and myelencephalon were investigated. Optimal stimulation frequencies varied from area to area and also were different for excitation and inhibition. Eliasson found that both inhibitory and excitatory responses could be obtained throughout the hypothalamus without specific localization. Points only 2 mm. apart gave opposite responses. He indicated an inhibitory response from the periaqueductal gray matter in his diagram of the mesencephalon.

The above material presents obvious disagreements as to the existence or nonexistence of definite excitatory (parasympathetic) or inhibitory (sympathetic) areas within the hypothalamus. Evidence of a different sort appears in the literature which offers support for the existence of separate regions. Keller[16] in 1936 and French and associates[17] in 1952 demonstrated that anterior hypothalamic lesions were associated with hemorrhages in the gastrointestinal tract, whereas posterior lesions were associated with ulcers. In both papers, the conclusion was drawn that the posterior region was sympathomimetic and the anterior region parasympathomimetic. The assumption was made that ulcers result from destruction of the posterior region due to the unchecked vagotonic action of the intact anterior region; the reverse being true for anterior lesions. Gellhorn and others,[18] using cardiovascular responses to drugs following lesions in either the anterior or posterior hypothalamus, reached a similar conclusion.

In the literature dealing with the relationship of the hypothalamus and midbrain to bladder motility, we find that Beattie[9] reported that direct stimulation of the lateral margins of the infundibulum gave rise to increased bladder tonus. Ranson and others,[19] using implanted electrodes, reported strong bladder contractions from stimulation of the septum and preoptic regions and throughout the lateral hypothalamus. They interpreted these bladder contractions as a parasympathetic response. The authors thought that the responses from the hypothalamus were due to stimulation of descending fibers. Beattie and Kerr[20] reported increased tonus from anterior hypothalamic stimulation and inhibition from posterior hypothalamic and rostral midbrain stimulation, thinking that this latter response was due to stimulation of descending fibers in the lateral margins of the periaqueductal gray matter. Conversely Kabat and associates[21] reported moderate, and occasionally severe, bladder contractions from the region of the periaqueductal gray matter as well as the hypothalamus. They stated that the bladder pathway from the caudal end of the mammillary body ran dorsally into the central gray matter and then caudally in the lateral margins of the periaqueductal gray matter and central tegmental fasciculus. Inhibitory responses were difficult to obtain and poor in quality. Wang and Harrison[22] reported good bladder contractions from anterior hypothalamic stimulation but also had difficulty in obtaining unequivocal bladder relaxation.

Magoun and associates,[23] investigating descending hypothalamic pathways, destroyed the central portion of the midbrain together with varying extents of the adjacent tegmentum and the medial longitudinal fasciculi. Although they reported some decrease in the responses elicited from hypothalamic stimulation, the effect was not as extreme as that obtained from destruction of both lateral mesencephalic regions, leaving the medial portion intact. On the basis of this, they concluded that the descending hypothalamic pathways were diffuse but tended to become concentrated laterally. In 3 cats, bilateral section of the lateral midbrain tegmentum and interpeduncular regions failed to prevent good bladder responses on hypothalamic stimulation. In other cats, lateral tegmental section did prevent bladder responses but the effect was not universal.

Uvnäs[24] in 1947 reported on the importance of the parameters of stimulation in studying bladder response. He found that high frequency stimulation (60 per second) gave relaxation, while low frequency stimulation (3 to 5 per second) caused contractions. How-

ever, both responses could be elicited throughout the hypothalamus, although the excitatory responses tended to be concentrated in the rostral end. He used chloralose as an anesthetic agent and concluded that other investigators had difficulty in obtaining inhibition because they used barbiturates which prevented spontaneous contractions of the bladder, thus making it difficult to note any inhibitory effects.

In a recent paper, Grossman and Wang,[25] reporting on the diencephalic mechanisms of control of the urinary bladder in the cat, seemed to confirm the previous conclusions of Ranson and associates[19] and Kabat and associates.[21] They obtained sustained bladder contractions from stimulation of the preoptic area, the septum pellucidum, the medial and lateral hypothalamus, the peripheral edges of the central gray matter of the midbrain, and the area about the central tegmental fasciculus. If lesions were made in the preoptic region, they could no longer obtain sustained bladder responses from the more caudal areas. This suggested to the authors that, in intact animals, sustained bladder responses arose from the preoptic and septal regions and that the more caudal responses were due to stimulation of descending connections. However, they were still able to obtain small unsustained contractions from stimulation of the ventromedial and posterior hypothalamic regions and the rostral midbrain. They commented that these responses were similar to those obtained from stimulation of the peripheral sympathetic supply to the bladder and suggested that these regions might represent central areas of sympathetic supply to the bladder exclusive of the more anterior parasympathetic areas.

MATERIALS AND METHODS

For these 2 investigations 52 cats were used:

1] A group of 31 acute cats in which a number of investigations were carried out, many of a preliminary nature not reported in this paper; 13 cats had multiple studies, including investigations of bladder motility.

2] A group of 7 acute cats in which both gastric motility and bladder motility were studied

3] A group of 14 cats in which chronic electrode placement and subsequent study of gastric motility was carried out.

In the first group of cats, 22 were given Nembutal anesthesia alone (25 to 30 mg. per kilogram) and 9 were given bulbocapnine (50 mg. per cat) and Nembutal (15 to 20 mg. per kilogram). With a modified Horsley-Clarke stereotaxic apparatus, the preoptic, hypothalamic, and periaqueductal gray regions were intensively stimulated with bipolar electrodes. These electrodes consisted of one 22- and one 28-gauge piece of insulated nichrome wire, cemented together and reinsulated. Their exposed tips were separated by 0.5 to 1 mm. A Grass stimulator, Model 3C, was used in 23 cats, and in 8, a biphasic square wave stimulator made by Mr. H. Teal of the Oxford University Laboratories of Physiology. A variety of frequency and duration parameters was explored. Although responses could be obtained over a wide range, the following 3 parameters most universally cover potential responsive areas: 5 cycles per second, 45 msec. duration; 74 cycles per second, 12 msec. duration; and 220 cycles per second, 6 msec. duration. Voltage strength was varied from 0.5 to 2.5. In these cats, bladder motility was recorded by an open technic. The bladder was exposed through a small suprapubic incision. A catheter was inserted into the bladder through a stab wound in the fundus and held by a purse-string suture. The abdominal wound was subsequently closed and bladder contractions recorded by a water manometer. After appropriate responsive areas in the rostral brain stem had been located, destructive lesions of the periaqueductal gray matter and/or the tegmental region were made. The same areas were then restimulated and modifications in bladder motility noted. Of 31 cats, 14 had only stimulation studies done and 17 had stimulation studies with subsequent destructive lesions and restimulation.

The second group of 7 acute cats was anesthetized with ether and then administered 50 mg. per kilogram of intravenous chloralose. At least forty-five minutes elapsed after the ether was stopped before any stimulation was carried out. The anterior hypothalamic region, tuberal region, lateral hypothalamic region, and periaqueductal gray region were stimu-

lated with the 3 frequency parameters mentioned above. The Oxford stimulator was used in this group. These cats were catheterized with a small polyethylene catheter which was connected to a closed saline-filled system terminating in a thistle tube. A rubber diaphragm was stretched over the open end of the thistle tube and a recording arm appropriately attached to this diaphragm. Increases in pressure in the system caused the diaphragm to bulge, and this movement was recorded on an ink writing hymograph by the recording arm. The thistle tube was placed at the approximate level of the bladder and the amount of fluid in the system controlled via a 3-way stopcock.

Gastric motility was recorded by an intragastric air-filled balloon. A Levin tube from the intragastric balloon was attached to one end of a U tube via an interposed airtight 3-way stopcock. The U tube contained a standard amount of bromoform. The gastric contractions were recorded on a kymograph by an ink-writing pen attached to a float riding on the surface of the bromoform in the opposite limb of the U tube. Through the 3-way stopcock, air in the intragastric balloon was allowed to come into equilibrium with atmospheric pressure to establish a base line; 50 cc. of air was then introduced into the balloon. The U tube and the amount of bromoform were kept standard in each experiment so that a valid comparison of the records could be made. A continuous base-line recorder was used on which the stimuli were marked.

In all the cats, destructive lesions of the periaqueductal gray matter and/or the tegmentum were made and changes noted in bladder and stomach responses to stimulation. Satisfactory lesions of the anterior two-thirds to three-fourths of the periaqueductal gray were produced by a straight wire electrode with a 1-mm. bare tip introduced by a stereotaxic apparatus. A series of 8 lesions, 4 on each side of the aqueduct, 1 mm. apart in the rostrocaudal direction, was made in each cat starting at a plane 4 mm. anterior to the zero coronal plane and proceeding caudally. A current of 5 ma. was allowed to flow for forty-five seconds at each of the 8 points. Lesions which extensively involved the adjacent tectum or tegmentum were discarded; however, the lesion could not be limited to the periaqueductal gray matter. Lesions which did not involve at least 75% of the circumference of the periaqueductal gray matter were also discarded.

The tegmental lesions were made in a similar manner, using the same type of electrode and current amplitude. In this case, a series of lesions—usually 7—was made in a lateral direction on the same coronal plane to destroy the tegmental area sparing the central periaqueductal gray and the peduncle. On one or both sides beneath the superior colliculus, 2 such series were made 1 mm. apart in the rostrocaudal direction.

At the end of each acute experiment in both groups, the animal was sacrificed and the brain prepared for histologic studies. The head was perfused with normal saline via the innominate artery followed by a solution of 10% formol saline. The brain was removed immediately and placed in a similar solution until prepared for sectioning. Paraffin imbedded blocks were serially sectioned at 10 μ; every fifteenth section was mounted. The sections were stained with either cresyl violet, or luxol fast blue and cresyl violet as recommended by Klüver and Barrera.[26] The points of stimulation and the extent of the lesions were determined from this material.

The group of animals with chronic implanted electrodes were investigated in the following manner: 6 cats had 2 bipolar electrodes implanted in the periaqueductal gray matter; each of the remaining 8 cats had 3 electrodes implanted in the hypothalamus—1 in the anterior, 1 in the middle (infundibulum), and 1 in the posterolateral hypothalamic area. In view of the size of the electrodes, only the general areas stimulated are indicated. To indicate that discrete nuclei were stimulated is unwarranted. The electrodes were placed through small bur holes in the skull under stereotaxic control and held securely in place by a cold curing acrylic plug. The peripheral ends of each bipolar electrode were separated and small solder balls affixed to them so that wires from the stimulating apparatus could be soldered in place at the time of stimulation.

At least a week was allowed to elapse after electrode implantation before stimulation studies were carried out. The Oxford stimulator was used. The same parameters and volt-

age strengths as described above were used, except for occasional variations within the limits of 5 to 220 cycles. Stimulus time varied from sixty to one hundred twenty seconds. Gastric motility was recorded under 50 mg. of bulbocapnine via an intragastric balloon. In 6 of these animals, gastric motility records were obtained before electrode implantation. Since no essential change occurred in the records after implantation in any of these animals, this control was considered unnecessary. Stimulation was started after thirty minutes of undisturbed gastric motility had been recorded.

After adequate stimulation records had been obtained on the 8 cats with electrodes in the hypothalamus, destructive lesions of the anterior two-thirds of the periaqueductal gray matter were made. The animals were allowed to recover for at least two weeks before postoperative stimulation records were obtained. These were carried out under as nearly similar conditions to the preoperative period as possible and at the same parameters and voltage strengths.

At the end of the experimental period, the animals were killed with an overdose of Nembutal and perfused in the manner described above. The appropriate areas were serially sectioned and stained alternately by the Klüver technic[26] and the modified Glees silver technic.[27]

RESULTS

For the purpose of analyzing the experimental results, all cats which had bladder motility studies will be considered together. Of 38 cats studied for bladder motility, 24 had subsequent destructive lesions of the periaqueductal gray matter and/or the tegmentum to observe the effects, if any, on the responses.

All cats showed bladder contractions on stimulation of the supraoptic and preoptic regions. In half the animals, responsive areas could be traced back through the hypothalamus to the supramammillary region. The periaqueductal gray matter was stimulated in 20 cats, but in only 3 were bladder contractions obtained. These contractions occurred on stimulation of the rostral portion of the central gray matter beneath the superior colliculus. Spontaneous bladder contractions occurred in 5 of the cats under chloralose anesthesia and in 3 under bulbocapnine and Nembutal. In none of these animals was inhibition obtained from any of the areas stimulated. Of the 8, 4 had destructive lesions made (2 periaqueductal and 2 tegmental) and the spontaneous contractions persisted after the lesions in all cases.

Lesions of the periaqueductal gray matter were made in 12 cats. Subsequent restimulation of previously located responsive areas revealed no change in response in 7 cats and a slight decrease in contraction strength in 5. In no cat was the bladder response prevented. In 7 cats, a unilateral destruction of the lateral tegmental region was done. Both ipsilateral and contralateral stimulations were then repeated. Ipsilateral stimulation caused no change in 3 cats, decreased response in 2, and no bladder response in 2. Contralateral stimulation was not influenced in any cat. Subsequent addition of a lesion on the other side resulted in bilateral changes in the 4 cats showing alterations—but still failed to prevent the response in the other 3. Examination of the stained sections revealed good destruction of both lateral tegmental regions and some involvement of the periaqueductal gray matter (Fig. 1).

In the remaining 5 cats, the periaqueductal gray matter had been destroyed with no effect and bilateral tegmental destruction subsequently added. In 3 cats, responses were still present after this, although decreased in strength, and, in 2 cats, the responses were prevented.

Stimulation of the cats with electrodes in the periaqueductal gray matter revealed the following findings. In 2 cats, no change occurred in gastric motility. In 2 others, stimulation at voltages of 2.5 caused the animals to move about and miaow. This activity was followed by a momentary cessation of gastric contractions. Cessation was not felt to be significant, since the same inhibition occurred after the animals *spontaneously* moved about and miaowed. In the remaining 2 animals, cessation of gastric motility without a drop in tension occurred following 1 v. stimuli at 36 cycles per second and 74 cycles per second. In 1 cat (G-8), the electrode was anteriorly placed and, in the other (G-12), it was more posterior (Fig. 2). These responses

could be reproduced on repeated stimulation.

In the cats with electrodes in the hypothalamus, the following results were obtained on stimulation in the prelesion period. Stimulation of the anterior region resulted in cessation of gastric motility with a slight drop in tension in 3 cats, no effect in 2, and a change in the character of the contraction in 3. This change was manifested by the appearance of small additional contractions at the peak of the regularly occurring large contractions, as illustrated in Figure 3. Such additional contractions also occurred spontaneously; however, their occurrence thirty to sixty seconds after stimulation in these 3 cats and the fact that their appearance could be reproduced on repeated attempts led the author to the conclusion that this represented an active response to stimulation.

Stimulation at the infundibular level resulted in cessation of gastric motility and decreased tone in all cats. Stimulation of the posterolateral area had no effect in 3 cats, produced in 4 a slight decrease in the height of gastric contractions without any change in rate, and produced in 1 a slight elevation in tension without alteration of motility.

After destructive lesions of the periaqueductal gray matter, stimulation of the infundibular region no longer caused inhibition (Figs. 4, 5, and 6). This was true of all cats. Inhibition from anterior hypothalamic stimulation was also prevented in 2 cats following periaqueductal gray matter destruction but could still be produced in a third animal. The production of additional contractions upon stimulation in the anterior region persisted; gastric motility was not affected by posterolateral stimulation in any cat.

In the 7 acute cats studied for gastric motility, the gastric contractions recorded under chloralose were smaller and more rapid than those obtained under bulbocapnine. With anterior hypothalamic stimulation, inhibition of gastric contractions with a slight drop in tension occurred in 3 cats, a slight increase in tone and rate in 2, and no effect in 2. In the 2 animals showing a slight excitation, the additional small contractions previously described also occurred thirty to sixty seconds after stimulation and lasted three to four minutes.

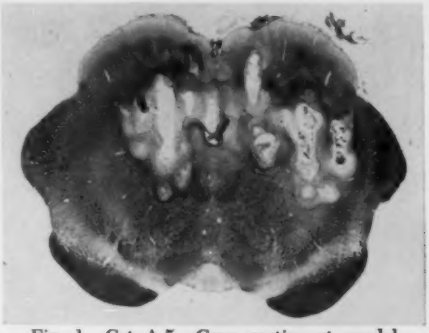

Fig. 1. Cat A-5. Cross section at caudal level of superior colliculus showing destruction of lateral tegmental region which is more extensive on the right than on the left. The periaqueductal region is also partially involved. (Luxol fast blue and cresyl violet × 9.5)

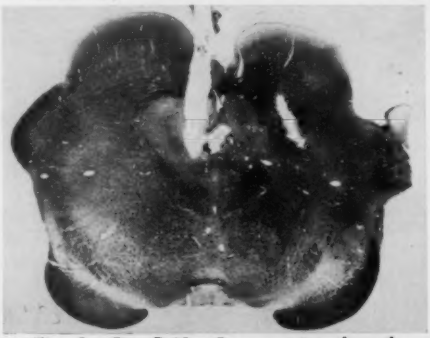

Fig. 2. Cat G-12. Cross section through caudal level of superior colliculus showing tract of chronic electrode in periaqueductal gray matter. (Luxol fast blue and cresyl violet × 9.5)

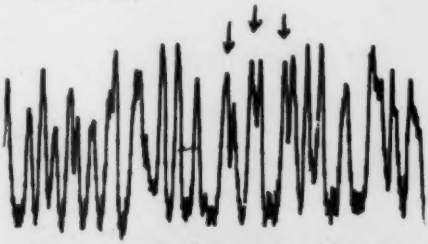

Fig. 3. A sample of the gastric motility record of Cat G-15. The arrows indicate the occurrence of additional contractions at the peaks of the normally occurring gastric contraction after stimulation of the anterior hypothalamic region.

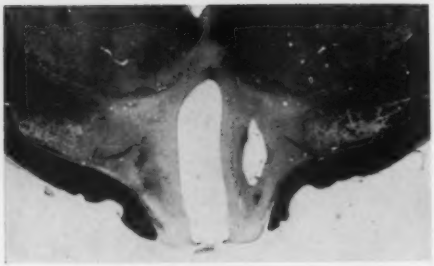

Fig. 4. Cat G-13. Cross section at anterior infundibular level cut somewhat obliquely to the tract of the electrode. Tract made by tip of chronic electrode in the hypothalamus is demonstrated. (Luxol fast blue and cresyl violet × 9.5)

Fig. 5. Cat G-13. Cross section at mid-superior colliculus level showing chronic destructive lesion of the periaqueductal gray matter in cat with chronic implanted electrodes in the hypothalamus. (Luxol fast blue and cresyl violet × 9.5)

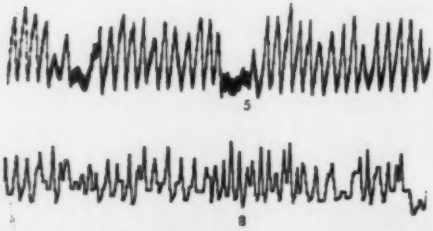

Fig. 6. Two sample gastric motility recordings. Cat G-13. Top record is prelesion and shows inhibition of gastric motility at 5 from stimulation of infundibulum at 74 cycles per second, 12 msec. duration and 1 v. Lower record is postlesion and shows lack of inhibition at 8.

Stimulation in the infundibular region (Fig. 7) resulted in inhibition in 5 cats and no effect in 2. Posterolateral stimulation caused cessation of gastric contractions and decreased tone in 4 cats and no effect in 3. Periaqueductal stimulation produced inhibition in 3 cats and no change in 4.

Subsequent destruction of the periaqueductal gray matter prevented inhibition from hypothalamic stimulation in all cats from all areas which had previously showed such a response—except from the anterior hypothalamic region in 1 cat. The slight increase in rate and tone could still be obtained on anterior hypothalamic stimulation in 2 cats. Subsequent addition of bilateral, lateral tegmental lesions in 5 of these cats caused cessation of all gastric activity in 3 and decreased activity in 2. Stimulation of the hypothalamic areas in these 2 cats did not alter the existing motility pattern.

DISCUSSION

The studies on bladder motility reported in this paper lend support to those authors[19-21,23] who found that stimulation in the anterior hypothalamic region and preoptic region gave rise to bladder contractions. Responsive areas could also be traced caudally through the hypothalamus. It has been further demonstrated that destruction of the periaqueductal gray matter did not prevent the elicitation of bladder contractions from the hypothalamus. This seemed to confirm the original impression of Magoun and associates[23] that the descending pathways for such responses were concentrated laterally. However, lateral tegmental destruction did not prevent the response in all cats, a finding also reported by the above authors. Although the majority of descending connections conducting bladder contractions may travel in the lateral tegmentum, the impression is formed that this is not universally true. Apparently, descending bladder pathways are quite diffuse.

Kabat and associates[21] reported bladder contractions upon stimulation of the periaqueductal gray matter; a finding which could be elicited in only 3 of 20 cats in the present series. The fibers described by these authors and Beattie and Kerr[20] in the periaqueductal gray matter must not be critical, since de-

Fig. 7. Cat A-3. Cross section through infundibulum in acute cat shows electrode tracts on either side in hypothalamus. (Luxol fast blue and cresyl violet × 9.5)

struction does not prevent bladder responses. In agreement with the report of Uvnäs,[24] the best bladder contractions occurred with low frequency stimulation (6 cycles per second). Inhibition could not be elicited with any of the parameters tested in the cats showing spontaneous contractions.

Only slight excitation of gastric motility could be obtained in a few cats on anterior hypothalamic stimulation. However, the anterior electrodes were just at the caudal edge of the optic chiasm.

The preoptic and septal regions were not explored in the animals in which gastric motility studies were done. In no cat was excitation elicited from the region of the tuber and infundibulum as reported by Beattie[9] and Beattie and Sheehan.[10] Inhibition was universally obtained from this region in all cats, and from the posterolateral region in about one-third of the cats. The anterior region did give rise to inhibition in an occasional animal. The material presented in this paper cannot offer any conclusive evidence for the existence, or lack of existence, of specific anterior excitatory or posterior inhibitory areas for gastric motility in the hypothalamus. The infundibular region, however, seems to be definitely inhibitory.

The most significant finding was the fact that destruction of the periaqueductal gray matter prevented inhibitory responses from the hypothalamus. However, in 2 animals, 1 chronic and 1 acute, inhibition from anterior hypothalamic stimulation was not prevented. No explanation can be offered for this. Despite the fact that periaqueductal gray matter destruction prevents inhibition, stimulation of the central gray matter caused inhibition in only 5 of 13 cats; however, excitation never occurred.

CONCLUSIONS

The periaqueductal gray matter does not carry a critical number of descending connections related to bladder contractions from the hypothalamus. These connections are diffuse and seem to run in the lateral tegmental area; however, even this region does not always carry a critical number. Pathways from the hypothalamus carrying gastric inhibitory impulses travel through the periaqueductal gray matter.

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Neurology

BOOK REVIEWS

Head Injuries Mechanisms, Diagnosis and Management

by E. S. Gurdjian and J. E. Webster, 482 pp., ill., Little, Brown & Co., Boston, 1958. $14

The physician who treats accidents every day wants a book to which he may refer for diagnostic and therapeutic help. Such a volume should present the subject clearly, concisely, and authoritatively; the practitioner is not in a position to evaluate the pros and cons of different opinions.

This monograph admirably fulfills these needs. Neurosurgeons who have had an extensive clinical and experimental experience with head injuries present their current viewpoints of the mechanism and treatment of head injuries. Not that other opinions are ignored – they are not – but they are not allowed to interfere with the authors' thesis. This makes for an easily read and harmonious presentation.

After a delightful historical introduction of the concept of head injuries, the authors present a brief account of the anatomy of cranial structures. The physical phenomena associated with blows to the head – so precisely studied by these authors in the past – are reviewed. This chapter is one of the best and most instructive in the book.

The remainder of the monograph presents in more or less orthodox fashion the clinical and laboratory manifestations of intracranial trauma with a discussion of its medical and surgical treatment. These chapters are particularly well illustrated. A brief discussion on medicolegal aspects of head injuries emphasizes the importance for the medical witness of a detailed, impartial, and objectively documented testimony regarding the head injury.

This is an excellent book; it has shortcomings – as has any treatise written by individuals with special personal interests. A more detailed discussion of the convalescence and rehabilitation of patients with head injuries would have added to the interest of the monograph for many physicians. Neurosurgeons and neurologists, in particular, will find this volume of lasting value.

A. E. W.

The Physiology and Pathology of the Cerebellum

Robert S. Dow and Guiseppe Moruzzi, 675 pp., ill., University of Minnesota Press, Minneapolis, 1958. $12.50

This is a monumental compendium of information on experimental and clinical physiology of the cerebellum by two men who have made important contributions to the investigation of the functional organization of the cerebellum. Part I deals with physiology, Part II with the clinical symptomatology and pathology.

Because of the rapid development of experimental investigations and the much slow-

er process of translation of the rapid advancement made in physiology into everyday clinical practice, the clinical part of the book probably stands a better chance to be of a lasting interest—especially to the clinical neurologist. The interest of Part I is that it summarizes and lucidly documents the strides made following the remarkable breakthrough in unraveling the development and organization of the cerebellum which has occurred since the pioneering work of Larsell in the 1920's and 1930's.

The book is, however, much more comprehensive in its scope than a summary of advancements made in the past quarter century. It is universal as a digest of the world literature on physiology and symptomatology of the cerebellum (57 pages of close print bibliography). The discussion of the arguments and of the experimental evidence reaches back into the early nineteenth century. However, the bulk of the text is concerned with the most recent discoveries and developments. The volume is a rich source of documentation and reference.

P. I. Y.

Über die Erblichkeit des normalen Elektroenzephalogramms, vergleichende Untersuchungen an Ein- und Zweieigen Zwilligen
(Heredity in Normal Electroencephalograms, A Study of Mono- and Dizygotic Twins)

F. Vogel, 92 pp., Georg Thieme Verlag, Stuttgart, Germany, 1958. $2.30

This is a meticulous analysis of the electroencephalograms of 208 pairs of twins—110 monozygotic and 98 dizygotic—from 6 to 30 years old. The tracings were made under resting conditions, stress (hyperventilation and oxygen-want), and sleep.

Studies of identical twins have been a popular method of investigating factors which may be hereditary. The electroencephalogram, being a relatively stable and readily analyzed phenomenon, has been used in many previous researches, usually with reference to epilepsy. This report, using objective criteria, inquires into the similarities and dissimilarities of the brain waves of twins.

In conformity with most previous reports, the characteristics of the electroencephalograms of identical twins are similar, while those of dizygotic twins differ in two-thirds of the cases. A great deal of detail is given regarding the analysis of the electroencephalogram under resting conditions, sleep, and stress.

A complete bibliography is appended. This book is recommended to those desiring a good account of the brain waves in twins. Its appeal to clinicians may be lessened by its technical treatment of the subject.

A. E. W.

The Excitable Cortex in Conscious Man

by Wilder Penfield, 42 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $2.50

In this small book, Penfield presents his credo on the function of the human cerebral cortex.

Penfield states that the application of an electrical current in threshold strength interferes with the normal function of the stimulated cortex and activates some distant, anatomical, related, ganglionic mechanism. On the basis of this assumption, Penfield interprets results obtained by stimulating visual, auditory, somatic sensory, motor, and temporal cortices. He concludes that whatever is appreciated in the sensory sphere must occur in the centroencephalic system—not in the cortex.

Neurologists will find this a handy reference—giving in general, but concise, terms Penfield's analysis of his stimulation of the cortex in human beings.

A. E. W.

Autonomic Imbalance and the Hypothalamus: Implications for Physiology, Medicine, Psychology, and Neuropsychiatry

by Ernst Gellhorn, 300 pp., ill., University of Minnesota Press, Minneapolis, 1957. $8.50

This monograph, as the subtitle indicates, is a study of relationship of the hypothalamus to laboratory and clinical medicine.

The book is divided into two sections: a larger part is devoted to experimental studies, and a shorter section correlates the studies with clinical problems. The first section is based on the extensive investigations of the

author and his colleagues. Direct and reflex stimulation of the hypothalamus, ablation technics, and pharmacologic methods were used to examine the relationship of the hypothalamus to autonomic reflexes and functions, the adrenal medulla, proprioception and the skeletal system, the viscera, respiration, and the cerebral cortex.

In an analysis of the sinoaortic reflexes, Dr. Gellhorn introduces the concept of tuning which constitutes a prominent part of his discussion. The applicability of Sherringtonian doctrines to the hypothalamus is underscored by descriptions of spatial and temporal summation, potentiation, sympathetic dominance and the analogy of flexor dominance in the somatic sphere, and successive autonomic induction. The second section of the book relates this experimental background to the intact organism. Particular reference is made to the studies of Wolf and Wolff, and of Funkenstein, as well as to the mecholyl test, the physiology of fear and anger, and the role of the hypothalamus in homeostasis.

From the data presented, the author suggests that a physiologic therapy of some of the functional psychoses might be envisioned. On the foundation of laboratory results, the integrated efforts of neurophysiologists, pharmacologists, psychiatrists, and psychologists may be able to increase our knowledge of brain functions, the physiologic basis of behavior, and therapy and prevention of functional psychosis. Dr. Gellhorn indicates that a great deal of work remains to be done but that "it is sufficient to have attempted great things."

S. L., M.D.
P. I. Y., M.D.

Epilepsy Handbook

Frederic A. Gibbs and Frederick W. Stamps, 101 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $4.75

This volume is a compact, practical compendium of knowledge about epilepsy. The authors have presented the material briefly and meaningfully, and the busy doctor will have little trouble in finding an answer to his problems.

A colored illustration of the drugs commonly used for treatment is very helpful.

Various types of epileptic seizures are considered, and an excellent section is included on conditions that may be mistaken for epilepsy—breath holding spells, strokes, tetany, hysteria, and so on. Drugs are considered in detail.

The last chapter is about counseling.

J.P.R.

Evolution of the Speech Apparatus

by E. Lloyd DuBrul, 103 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $4.75.

This small volume proposes that, to understand speech, one must study the historic continuum that preceded the human speech apparatus.

Throughout this continuum, numbers of symmetrical parts subserving the same function have been progressively reduced. Thus, the earliest animal forms used multiple segments for locomotion; 2 sets of lateral fins developed in fish, and 2 sets of legs for locomotion developed in reptiles and mammals. Later, the number of sets used for locomotion was reduced to 1 and the erect posture was assumed. The upper extremities were freed for procuring and preparing food. The mouth, freed of these tasks, became available for speech.

With the assumption of erect posture, the neck was moved forward and the airway and foodway were forced to take on a progressively greater angle. The larynx was removed from close proximity to the nasopharynx and could occasionally be closed. This allowed the expired air to be diverted through the flexible oral cavity where it could be shaped into a wide variety of sounds. In man, these peripheral anatomic rearrangements permitting speech occurred at a time when brain development was adequate for speech and when social integration required it.

This book is interesting and informative. The illustrations serve well to support the author's proposition. It is a little disappointing, though understandable, that the peripheral speech apparatus was not related more closely to changes in the central neural structures.

J. R. B.

Program of the American Academy of Neurology

Eleventh Annual Meeting

April 16-18, 1959

Statler Hilton Hotel, Los Angeles

THIS YEAR the general scientific program will be held in the Golden State Room in 4 sessions: Thursday morning, April 16; Thursday afternoon (jointly with Child Neurology), April 16; Friday afternoon, April 17; and Saturday morning, April 18.

Business meetings of the Academy will be held in the Golden State Room at 5:20 P.M., Friday, April 17, and 12 noon Saturday, April 18. There will be 3 special section meetings: Child Neurology, Thursday afternoon, April 16, in the Golden State Room; a joint meeting of Neurochemistry and Neuropharmacology, Thursday afternoon, April 16, and Friday morning, April 17, in the Los Angeles Room; Neuroanatomical Sciences, Thursday afternoon, April 16, in the East Garden Room and Friday morning, April 17, in the Golden State Room.

A symposium on Myasthenia Gravis, sponsored by the Myasthenia Gravis Foundation, will be held Saturday morning, April 18, in the Los Angeles Room and Saturday afternoon, April 18, and Sunday morning and afternoon, April 19, in the Los Angeles Room.

The programs for these meetings are listed.

General Scientific Session, Thursday, April 16, 1959

Morning session: 9 A.M.
Chairman: Robert B. Aird, *San Francisco*
Secretary: Donald Macrae, *San Francisco*

S. Weir Mitchell Award Essay

Subject and author to be announced. This is the annual award given by the Woman's Auxiliary of the American Academy of Neurology to the junior member who submitted the manuscript adjudged best by the committee.

The Development of Cerebral Atherosclerosis in Various Age Groups

John Moossy, *New Orleans*

Anticoagulants in Cerebral Thrombosis

Charles M. Fisher, Herbert R. Karp, and M. Sadka, *Boston*

Anticoagulant Therapy in Cerebral Vascular Disease: The Problems of Long-Term Administration

Sigmund N. Groch, L. Hurwitz, Ellen McDevitt, and Irving S. Wright, *New York City*

Correlation of Neurologic Syndromes of Cerebral Arterial Insufficiency with Arteriographically Demonstrated Extracranial Lesions

William S. Fields, Paul C. Sharkey, E. Stanley Crawford, and Curtis H. Burge, *Houston*

Dissecting Aneurysms of Intracranial Arteries

George E. Scott, John B. Denst, and Karl T. Neubuerger, *Denver*

The Blood Viscosity in Cerebrovascular Disease

Roy L. Swank, *Portland, Ore.*

Effects of Changes in Composition of the Plasma on Pial Blood Flow

John S. Meyer and Arthur G. Waltz, *Detroit*

The Neurologic Aspects of Temporal Arteritis

Robert W. Hollenhorst, Joe R. Brown, Henry P. Wagener, and Richard M. Shick, *Rochester, Minn.*

The Neural Lesion in Necrotizing Arteriolitis

George W. Holt and Charley J. Smyth, *Denver*

A Clinical, Electroencephalographic, and Pathologic Study of Patients Undergoing Open Heart Surgery

Maynard M. Cohen, Gilbert Frank, C. Walton Lillehei, and Fernando Torres, *Minneapolis*

Quantitation of Tone, Tremor, Voice, and Movement in the Normal and in Parkinsonism

Benjamin Boshes, Joel Brumlik, Hirsh Wachs, Manuel Mier, and Mathew L. Petrovick, *Chicago*

Dynamic Measurement of Rigidity, Strength, and Tremor in Parkinson Patients Before and After Destruction of the Mesial Globus Pallidus
David D. Webster, *Minneapolis*

Tests of Motor Performance in Parkinson's Disease: Limitations, Errors, and Values; A Twelve-Year Report
William H. Timberlake and Robert S. Schwab, *Boston*

General Scientific and Section of Child Neurology Session, Thursday, April 16

Afternoon session: 2 P.M.
Chairman: Richard L. Masland, *Bethesda, Md.*
Secretary: Philip Dodge, *Boston*

Development of Reticulocortical Control in the Newborn
Madge E. Scheibel and Arnold B. Scheibel, *Los Angeles*

The Anatomical Patterns Related to the Reflexes Elicited by Double Simultaneous Stimulation Tests of Human Fetuses
Tryphena Humphrey and Davenport Hooker, *Pittsburgh*

Multiple Sensory Stimulation Findings in Children with Disorders of Behavior
Frederick W. Maire and Margaret A. Kennard, *Fort Steilacoom, Wash.*

Symptoms and Diagnosis of Diastematomyelia
George E. Perret, *Iowa City*

Progressive Ataxia in Childhood with Particular Reference to Ataxia-Telangiectasia
Robert P. Sedgwick and Elena Boder, *Los Angeles*

Course and Prognosis of Acute Cerebellar Ataxia in Children
Stuart Weiss and Sidney Carter, *New York City*

Maple Syrup Disease
John H. Menkes, *New York City*

Myoclonic Seizures in Infancy Associated with the Excretion of an Abnormal Aromatic Metabolite
Richard J. Allen and Eldon H. Sutton, *Ann Arbor, Mich.*

Studies in Metachromatic Leucoencephalopathy
James H. Austin, *Portland, Ore.*

A Case of Atonic Cerebral Diplegia with Lissencephaly
Ralph I. Druckman, Dora Chao, and Ellsworth C. Alvord, Jr., *Houston*

Infectious Neuronitis in Children
Albert F. Peterman, David D. Daly, and Haddow M. Keith, *Rochester, Minn.*

Diffuse Sclerosis; Krabbes (globoid) Type
Richard G. Berry and William T. McLean, *Philadelphia*

Cerebral Palsy of Von Bogaert-Bertrandt Type: A Neuropathological and Clinical Description
Gabriele M. Zu Rhein, Peter L. Eichman, and Flavio Puletti, *Madison, Wis.*

General Scientific Session Afternoon Meeting, Friday, April 17, 1959

Afternoon Session: 2 P.M.
Chairman: Fred Plum, *Seattle*
Secretary: August Swanson, *Seattle*

Presidential Address
Francis M. Forster, *Madison, Wis.*

Vertiginous Disturbances in Epilepsy
Bernard H. Smith, *Buffalo, N. Y.*

Tornado Epilepsy
Johannes M. Nielsen, *Los Angeles*

Prolonged Behavioral Changes as Ictal Phenomena
Eli S. Goldensohn and Arnold P. Gold, *New York City*

Development of Ideas Relating the Mind with the Brain
Horace W. Magoun, *Los Angeles*

An Inquiry into the Causes of Polyuria and Polydypsia in Patients with Injuries to the Cervical Portion of the Spinal Cord
Meyer Brown, Stanley W. Pyzik, and John R. Finkle, *Evanston, Ill.*

An Evaluation of Graded Hypophysectomy in Man
John M. Van Buren and Delbert M. Bergenstal, *Bethesda, Md.*

The Incidence and Type of Pathologic Alterations in Striated Muscle Obtained from Routine Autopsies
Carl M. Pearson, *Los Angeles*

Huntington's Chorea in Michigan (1900-1955)
Joseph H. Chandler, T. Edward Reed, and Russell N. De Jong, *Ann Arbor, Mich.*

A Clinical and Pathological Study of Akinetic Mutism
Humberto Cravioto, Jacobo Silverman, and Irwin H. Feigin, *New York City*

Some Features of the Pathogenesis of Myotonia
N. I. Grashchenkov, *Moscow*

Business Meeting, 5:20 P.M.
Francis M. Forster, *President*, presiding

General Scientific Session, Saturday, April 18, 1959

Morning Session: 9 A.M.

Chairman: Roy L. Swank, *Portland, Ore.*

Secretary: James Austin, *Portland, Ore.*

Determination of Topological Human Brain Representations and Modifications of Signs and Symptoms of Some Neurologic Disorders by the Use of High Level Ultrasound
H. Russell Meyers, Frank J. Fry, William J. Fry, Reginald C. Eggleton, and Donald F. Schultz, *Iowa City,* and *Urbana, Ill.*

Electrophysiological Study of Cortical and Spinal Cord Lesions in Cats with Allergic Encephalomyelitis
Roger M. Morrell, *Montreal*

Proprioceptive and Cerebellar Control of Vestibulospinal Influences
Sid Gilman and Bo E. Gernandt, *Bethesda, Md.*

Brain Stem Action Potentials Correlated with Eye Movements
Howard P. Krieger, *New York City*

The Formation of Temporary Cerebral Connections in Normal and Brain-Damaged Subjects
Charles E. Wells and Harold G. Wolff, *New York City*

Collateral Circulation to the Spinal Cord Studied by Autoradiography
Eiichi Otomo, *Baltimore*

Changes in Spinal Fluid and Vascular Pressures Associated with Hyperosmolarity
Lois P. Drawdy, Charles N. Luttrell, and Laurence Finberg, *Baltimore*

Alterations in Pulmonary Function in Myotonic and Progressive Muscular Dystrophy
Albert Heyman, Kaye H. Kilburn, John T. Eagen, and Herbert O. Sieker, *Durham, N. C.*

Familial Hemiplegic Migraine
Herbert E. Rosenbaum, *St. Louis*

Effect of Serotonin on Migraine Patients
Robert W. Kimball, Arnold P. Friedman, and Edward Vallejo, *New York City*

Hereditary and Idiopathic Cerebellar Degenerations
Joe R. Brown, *Rochester, Minn.*

Meningeal Tumors with Extracerebral Metastasis
Francis Kruse, Jr., *Washington, D. C.*

Business Meeting 12 Noon
Augustus S. Rose, *President*

Section of Neuroanatomical Sciences Separate Meeting, Thursday, April 16, 1959

Afternoon session: 2 P.M.

Chairman: Alphonse R. Vonderahe, *Cincinnati*

Photoreception versus Phonoreception
M. Wharton Young, *Washington, D. C.*

Injury to the Nervous Tissue Produced by Intracarotid Injection of Alcohol
Jerzy Olszewski and B. Rozdilskyi, *Saskatoon, Canada*

The Glia/Neuron Index in the Submolecular Motor Cortex in the Cat
Kenneth R. Brizzee, *Salt Lake City*

The Proteolipide Nature of the Neurokeratin Network and Its Tinctorial Properties
Harold Koenig, *Chicago*

Cyst Formation in the Cerebral White Matter
Cyril B. Courville, *Los Angeles*

Results of Long Survival after Thrombosis of the Superior Sagittal Sinus
Orville T. Bailey, *Indianapolis*

Reinnervation of the Diaphragm by Vagus and Recurrent Laryngeal Nerves
Lloyd Guth and Karl Frank, *Bethesda, Md.*, Lamar Soutter, *Boston,* and James B. Campbell, *New York City*

Relation of Millipore® to Healing and Regeneration in Transected Spinal Cords of Monkeys
James B. Campbell, *New York City,* and William F. Windle, *Bethesda, Md.*

The Brain Stem Reticular Core: Diencephalic Components
Arnold B. Scheibel and Madge E. Scheibel, *Los Angeles*

A Study of Septal Stimulation and Ablation in the Monkey
Charles L. Votaw, *Ann Arbor, Mich.*

Histogenesis of the Trigeminal Sensory Root in Rats during the Period of Development of Red Fluorescence
Ivan Diamond and Ruth Rhines, *Chicago*

Capillary-Neuron Relationship in the Central Nervous System
Edward G. Bertram, Harry K. Ihrig, and G. Williams, *Milwaukee, Wis.*

X-Ray Radiation of Experimental Lesions of the Spinal Cord
Calvin C. Turbes, Leslie W. Freeman, and David C. Gastineau, *Indianapolis*

Behavioral and Histopathological Effects of Brain X-Irradiation in Immature Rats
Carmine D. Clemente, J. Yamazaki, L. Bennett, and R. McFall, *Los Angeles*

The Significance of Field Effects and Pharmacological State in Recording Optic Potentials from Cat Cerebellum
C. M. Berry, J. S. Haft, P. M. Harman, and Christian A. Hovde, *Jersey City, N. J.*

Regeneration Across the Gap in the Transected Adult Feline Spinal Cord: Early Morphologic Findings
Charles R. Noback, C. Andrew Bassett, Jakob Husby, Carl A. Thulin, and James B. Campbell, *New York City*

Friday, April 17, 1959

Morning session: 9 A.M.
Symposium on the Rhinencephalon
Chairman: Ray S. Snider, *Chicago*

Some Neural Pathways Related to the Limbic System
Walle Nauta, *Washington, D. C.*

Some Recent Physiological and Cytological Observations on Ammon's Horn
John Green and David Maxwell, *Los Angeles*

The Rhinencephalon of the Shrew (Sorex cinereus)
Berry Campbell, *Los Angeles*

Recent Studies of Interrelations of Rhinencephalic Areas with Subcortical Structures
W. Ross Adey, *Los Angeles*

Microelectrode Studies in the Rhinencephalon During Conditioning
Frank Morrell, *Minneapolis*

A Behavioral Analysis of the Effects of Ablation of Some Rhinencephalic Structures
Karl Pribram, *Hartford, Conn.*

Experimental Problem Pertaining to Korsakoff's Syndrome
Paul McLean, *Bethesda, Md.*

Discussors will be:
W. Ross Adey, Berry Campbell, John Green, Paul McLean, Frank Morrell, Karl Pribram, and Ray S. Snider

Sections of Neurochemistry and Neuropharmacology (Joint Meeting), Thursday, April 16, 1959

Afternoon session: 2 P.M.
Chairman: Maynard M. Cohen, *Minneapolis*
Secretary: Beni Horvath, *Bethesda, Md.*

In Vivo Levels and Relative Specific Activities (R.S.A.) of Brain Phosphate Fractions of Normal and Scorbutic Guinea Pigs
Sping Lin and Harold P. Cohen, *Minneapolis*

Chemical Concomitants of Convulsive Activity in the Cerebrum
William E. Stone and J. K. Tews, *Madison, Wis.*

Cholesterol and Fatty Acid Synthesis in Diabetic Nerve and Spinal Cord
Sven G. Eliasson and Ann H. Hughes, *Dallas*

Interaction of Viruses with Native Brain Substrates
Samuel Bogoch, *Boston*

Some Aspects of Tricarboxylic Acid Cycle Metabolism in the Central Nervous System
John Potanos, Aaron D. Freedman, and Samuel Graff, *New York City*

Myelin Enzymes in Wallerian Degeneration
Frederick J. Wolfgram, *Los Angeles*

Immunochemical Studies on Muscle Proteins
Beni Horvath, *Bethesda, Md.*

Electron Microscope Study on the Function of Astroglia in the Water Ion Metabolism of the Central Nervous System
H. M. Gerschenfeld, F. Wald, J. A. Zadunaisky, and Eduardo DeRobertis, *Buenos Aires*

Magnesium and Central Nervous System Metabolism
Jack H. Mendelson, June E. Mendelson, Benjamin A. Barnes, and Philip Solomon, *Boston*

The Effect of Acetazoleamide (Diamox) on EEG Abnormalities Induced by Hypernatremia and H_2O Excess
August G. Swanson, *Seattle*

Sections of Neurochemistry and Neuropharmacology, Friday, April 17, 1959

Morning session: 9 A.M.
Chairman: William K. Jordan, *Little Rock, Ark.*
Secretary: Maynard M. Cohen, *Minneapolis*

A Survey of Cerebrospinal Fluid Glutamic Oxaloacetic Transaminase Activity in Neurological Syndromes
Stuart H. Mann, Nicholas P. DePasquale, and Ruth Paterson, *New Orleans*

Abnormal Protein Fractions of Cerebrospinal Fluid in Neuropsychiatric Diseases
Henn Kutt and Fletcher H. McDowell, *New York City*

Vitamin Levels in Cerebrospinal Fluid in Normals and in Neurological Disorders
Harry H. Sobotka, Herman Baker, and Israel S. Freiman, *New York City*

Cerebrospinal Fluid Formation and Cerebral Metabolism
Edgar A. Bering, Jr., *Boston*

Preliminary Observations on Abnormal Catechol-amine Metabolism in Diseases of the Basal Ganglia
André Barbeau, *Chicago*

Wilson's Disease: The Presence of Hypercalciuria and the Urinary Excretion of Calcium and Copper after Administration of DL-Penicillamine
Robert B. Litin, Raymond V. Randall, Marschelle H. Power, Grant R. Diessner, and Norman P. Goldstein, *Rochester, Minn.*

A Cutaneous Mucopolysaccharide in Amyotrophic Lateral Sclerosis
Harold M. Fullmer, Leonard T. Kurland, and Howard D. Siedler, *Bethesda, Md.*

The Localization of Actylcholinesterase within the Cochlea
Harold F. Schuknecht and John A. Churchill, *Detroit*

The Experimental Production of "Motor Neuron Disease" with a Nucleic Acid Antimetabolite
Harold Koenig, *Chicago*

Progressive Dementia, Myoclonus, and Periodic EEG; A Variant of Jakob-Creutzfeld
R. Katzman, H. Zimmerman, E. Kagan, Saul R. Korey, and J. Orloff, *New York City*

Effect of Chlorpromazine on Hypothalamic "Rage" in the Cat
Murray Glusman and Joseph Ransohoff II, *New York City*

READ BY TITLE

The Treatment of Tetanus with the Phenyl Radical
Leo J. Adelstein, *Los Angeles*

Myoclonus: Its Clinical Significance and an Approach to Classification
B. Robert Aigner, Donald W. Mulder, and David Daly, *Rochester, Minn.*

Angiographic Significance of the Posterior Cerebral Artery
Marshall B. Allen, Jr., and Orlando J. Andy, *Jackson, Miss.*

Diphenylhydantoin Therapy of Trigeminal Neuralgia
Kittridge Anderson, Joseph F. Dorsey, and Gordon W. Hayslip, *Boston*

Acute Brain Stem Lesion Effects upon Seizures
Orlando J. Andy and J. Mukawa, *Jackson, Miss.*

Subacute Combined Degeneration Due to Vitamin B-12 Deficiency Without Anemia
Robert N. Baker, *Los Angeles*

Anatomical Contribution to the Etiology of E. M.
L. Barraquer-Ferré, *Barcelona, Spain*

Double Compression of Cauda Equina Produced by a Free Distal Herniation
Luis Barraquer-Ferré, *Barcelona, Spain*

Low Spinal Fluid Pressure Syndrome
William E. Bell, Robert J. Joynt, Jr., and Adolph L. Sahs, *Iowa City*

Effect of a Convulsant Drug in Patients with Structural Lesions of the Brain
Bernard Cohen, Jean Rey-Bellet, and Philip S. Bergman, *New York City*

Pitfalls in Diagnosis of Lumbosacral Neuritis
Arthur Biddle and Nicholas Wetzel, *Seattle*

Correlation of the Clinico-Pathologic Findings and Electroencephalographic Abnormalities in Cerebral Infarction Due to Atherosclerosis
Richard I. Birchfield, William P. Wilson, and Albert Heyman, *Durham, N. C.*

Behcet's Syndrome with Neurological Manifestations: Report of a Case
Irving J. Blumenthal, *Northport, N. Y.*

Personal Experience of 516 Percutaneous Carotid Angiograms
Robert J. Brocker, *Pittsburgh*

Savor
Edward C. Clark, *Rochester, Minn.*

Neurological Management of "Low-Back Syndromes"
David R. Coddon and Julius Korein, *Travis Air Force Base, Calif.*

Atherosclerotic Aneurysms of the Larger Intracranial Arteries
Cyril B. Courville, *Los Angeles*

Factors Influencing Late Prognosis of Cerebral Infarction Due to Atherosclerosis
Noble J. David and Albert Heyman, *Durham, N. C.*

Myasthenia Gravis Associated with Malignant Thymoma: A Four Year Follow-up
Sherwood Davidson and Artur Abramowicz, *Boston*

The Neurologic Sequelae of "Whiplash" Injury
Harold Dillon and Robert L. Leopold, *Philadelphia*

Acute Encephalopathy in Water Intoxication
Samuel H. Epstein, *Boston*

The Pathogenesis of Symptoms Resulting from Cerebral Concussion
Maurice D. Friedman, *Cleveland*

Objective Circulatory Dysfunction in Head Injury
Anthony R. Furmanski, *Van Nuys, Calif.*

Familial Amyotrophic Lateral Sclerosis
John H. Gardner and Paul H. Garvey, *Rochester, N. Y.*

Hereditary Sensory Radicular Neuropathy: An Extension of the Syndrome
Norman Geschwind, *Boston*

The Subcommissural Organ in Man
Gordon J. Gilbert, *New Haven, Conn.*

Observations on Nerve Conduction in Hereditary (Friedreich's) Ataxia
William L. Harlan, *Galveston*

Carotid Artery Occlusive Disease Diagnosis and Natural History
L. J. Hurwitz, Sigmund N. Groch, and Fletcher McDowell, *New York City*

Competitive Interaction of Cortex and Brainstem on Ocular Movements in Cats
W. B. Jennett and J. E. Hyde, *Los Angeles*

The Diagnostic Implications of Slow Activity in the Electroencephalogram
Robert J. Joynt and John R. Knott, *Iowa City*

Circulatory and Electroencephalographic Changes Associated with Loss of Consciousness in Vasodepressor Syncope
Herbert R. Karp, Arnold M. Weissler, and Albert Heyman, *Durham, N. C.*

Thermodynamics, Information, and the Neurophysiology of Behavior
Julius Korein, *Travis Air Force Base, Calif.*

Vector Analysis of Slow Wave Forms of the Brain
Le Roy Kurth, Desmond S. O'Dogherty, and Patrick F. O'Connell, *Washington, D. C.*

A Study of Pulmonary Function in Parkinson's Disease
Harold A. Ladwig, Harold N. Neu, Jr., John J. Connelly, Jr., Frederick J. Schwertley, and Alfred W. Brody, *Omaha*

Central Gangliocytomas
Leopold Liss, *Ann Arbor, Mich.*

What Is Tic Douloureux?
Carl F. List, *Grand Rapids, Mich.*

An Evaluation of the New Anticonvulsant Elipten
Herbert L. Martin, Antonio Aquilar, and Francis McNaughton, *Burlington, Vt.*

A Cooperative Study of Cerebral Vascular Disease; Preliminary Report
Ellen McDevitt, S. N. Groch, and Irving S. Wright, *New York City*

An Arteriographic Study of Cerebrovascular Disease
Fletcher McDowell, Robert W. Schick, William C. Frederick, and Howard S. Dunbar, *New York City*

The Electroencephalogram in Internal Carotid Artery Occlusion
Fletcher McDowell, Charles E. Wells, and Carol Ehlers, *New York City*

Experiences with Chemical Rhizotomy
Sedgwick Mead, *Vallejo, Calif.*

Pulmonary Changes in Hydantoin Therapy
Matthew T. Moore, *Philadelphia*

Genetic Counselling in Neurology
Ntinos Myrianthopoulos and Harold Stevens, *Washington, D. C.*

The Intracerebral Injection of Cholinergic and Anticholinergic Drugs in Man
Blaine S. Nashold, Jr., *Durham, N. C.*

Diagnostic Problems of Muscular Weakness and Atrophy in Infants and Children
Max K. Newman, *Detroit, Mich.*

Clinico-pathological Significance of Anatomical Variations in the Arteries of the Base of Brain
Shigeo Okinaka, Masakuni Kameyama, and Tadao Tsubaki, *Tokyo*

The Diagnostic Problem of Epilepsy of Late Onset
Richmond S. Paine, *Boston, Mass.*
Richard B. Raynor, *New York City*, and E. Arnold Carmichael, *London, England*

Epilepsy in Childhood
Mynie G. Peterman and Elaine M. Thomas, *Milwaukee*

Copper Diuresis in Epilepsy and Dilantin Intoxication
Henry A. Peters, Frank L. Kozelka, and N. M. Moore, *Madison, Wis.*

Mesantoin in the Treatment of Acute Chorea
Gustavo F. Poch, *Buenos Aires*

Polymyositis as the First Symptom Complex in Scleroderma
Gustavo F. Poch, *Buenos Aires*

Prognosis in Subarachnoid Hemorrhage
Seymour L. Pollack and Richard M. Paddison, *New Orleans*

The Electroencephalogram in Migraine
Charles M. Poser and Dewey K. Ziegler, *Kansas City, Kan.*

The Treatment of Barbiturate Poisoning
Jerome B. Posner and Fred Plum, *Seattle*

Positional Nystagmus
Francis J. Schiller and William C. Hedberg, *San Francisco*

The Relation of Certain Diagnostic Features of Internal Carotid Occlusion to Collateral Circulation
Allen Silverstein, Gerard M. Lehrer, and Robert J. Mones, *New York City*

Noise in the Pupil Servomechanism
Laurence Stark, J. Atwood, and F. W. Campbell, *New Haven, Conn.*

A Ten Year Investigation of 75 Patients with Multiple Sclerosis: Diagnostic, Laboratory, and Therapeutic Aspects
Frederick D. Stern and Leon Roizin, *New York City*

A Psychological Study of Temporal Lobe Epilepsy
Janice R. Stevens and Victor Milstein, *Portland, Ore.*

Conditional Salivary Reflex in Clinical Studies
George F. Sutherland, *Baltimore*

Section of Dentate Ligament in the Treatment of Arterial Anomaly of the Spinal Cord
Paul Teng, *Los Angeles*

Section of the Scalenus Anticus as a Treatment to a Certain Type of Hemicranial Pain: A Clinical Study of Twenty Cases
Paul Teng, *Los Angeles*

A New Rating Method for Multiple Sclerosis
Melvin W. Thorner, *Philadelphia*

The Influence of Head Position upon Flow Through the Vertebral and Internal Carotid Arteries: A Post-Mortem Study
James F. Toole and Samuel H. Tucker, *Philadelphia*

Meprobamate Poisoning
Louis L. Tureen and Joseph B. Kendis, *St. Louis*

Hypercholesterolemia and "Strokes" in Young Adults
R. A. Utterback and R. C. Hardin, *Iowa City*

The Physiological Effects of Phenothiazines on the Central Nervous System
Francis A. Vazuka, Leon Saunders, Richard Steelman, Robert Sekella, and Erminio Arena, *Philadelphia*

Chronic Experimental Epilepsy; Behavioral and Electrographic Manifestations
John Wada and Leigh R. Cornellus, *Vancouver*

The Mind-Body Dilemma in the Treatment of Emotionally Disturbed Epileptics
Charles Watkins, Marvin Miller, and Carl Davis, *New Orleans*

The Myotonias; a Report of Successful Treatment with Fever Therapy
Ward W. Woods and Paul A. Shea, *San Diego*

Experimental and Therapeutic Aspects of Cortical Ischemia
Stanislaw A. Ziemnowicz, *Washington, D. C.*

Urea for Reduction of Intracranial Pressure
Manucher Javid, *Madison, Wis.*

The Second International Symposium on Myasthenia Gravis

April 18 and 19, 1959

Statler Hilton Hotel, Los Angeles

Saturday, April 18, 1959

Morning session: 9:00 A.M.
Moderator: Robert S. Schwab, *Boston*
Introductory Remarks: Henry R. Viets, *Boston*

Current Studies Covering Anatomy, Physiology and Biochemistry

The Normal Neuromuscular Junction

The Ultrastructure of the Mammalian Neuromuscular Junction and Localization of Cholinesterase
Gerard M. Lehrer, *St. Louis*

Electrical and Mechanical Events in Neuromuscular Transmission and Muscle Contraction
Richard J. Johns, *Baltimore*

Factors Influencing the Response of Intact Human Muscle to Synchronous Efferent Volleys
Irving H. Wagman and Daniel S. Feldman, *New York City*

Electrical Activity of Mammalian Muscle Studied by Microelectrodes: Effects of Electrolyte Alterations
John T. Conrad and Gilbert H. Glaser, *New Haven, Conn.*

Chemical Events in Muscular Contraction
(The Henry R. Viets Lecture)
Wilfried F. H. M. Mommaerts, *Los Angeles*

The Role of Muscle and Plasma Cholinesterase in Neuromuscular Block
Richard L. Irwin and Jay B. Wells, *Bethesda, Md.*

Effects of Venoms on Neuromuscular Transmission
Findlay E. Russell, *Los Angeles*

The Neuromuscular Junction in Myasthenia Gravis

The Production of Myasthenic State in Man and Its Possible Significance for the Pathogenesis of Myasthenia Gravis
Francis F. Foldes, *Pittsburgh*

Further Studies on the Mechanism of Defects in Neuromuscular Transmission
David Grob, *Brooklyn*, and Richard J. Johns, *Baltimore*

The Neuromuscular Defect in Myasthenia: Electrophysiological and Histopathological Evidence
J. E. Desmedt, *Brussels, Belgium*

Saturday, April 18, 1959

Afternoon Session: 2:00 P.M.
Moderator: Kermit E. Osserman, *New York City*

Some Pathophysiological Mechanisms of Motor Disturbances in Myasthenia
N. I. Grashchenkov and L. B. Perelman, *Moscow*

Electromyographic Studies in Myasthenia Gravis Correlated to Mechanical Events
Albrecht Struppler and Elizabeth Struppler, *Munich*

A Study of Neuromuscular Transmission in 100 Cases of Myasthenia Gravis
Harry C. Churchill-Davidson and Arthur T. Richardson, *London, England*

Possible Mechanisms in Myasthenia Gravis

In Vitro Muscle Biopsy Techniques for Study of Myasthenia Gravis
John B. Dillon, Christian Herrmann, Jr., Wiley F. Barker, and Phiroze Sabawala, *Los Angeles*

Preliminary Report on the Effect of Myasthenia Gravis Serum on the Neuromuscular Transmission of the Intact Frog
Charles E. Windsor, *Rochester, N. Y.*

Humeral Factors in the Causation of Myasthenia Gravis
William L. Nastuk and Arthur J. L. Strauss, *New York City*

The Isolation of Quaternary Nitrogen Compounds from Extracts of Thymus Glands
Peter T. Nowell and Andrew Wilson, *Liverpool, England*

Some Pharmacologic Properties of Gamma Butyrobetaine
E. A. Hosein, Emma Ottolenghi, and Sheila Dorfman, *Montreal*

Recent Work on the Mechanism of Myasthenia Gravis, with Special Reference to the Metabolism of Progesterone
Raymond Greene and Isadore Schrire, *London, England*

Comparison of Digitalis and Veratrum Steroids on Human Skeletal Muscle, with Reference to Myasthenia Gravis
William W. Hofmann, *San Francisco*

Sunday, April 19, 1959

Morning session: 9 A.M.
Moderator: Robert B. Aird, *San Francisco*

Present Clinical Problems of Myasthenia Gravis

Incidence

Current Knowledge of the Epidemiology and Genetics of Myasthenia Gravis
Leonard T. Kurland and Milton Alter, *Bethesda, Md.*

The Incidence of Myasthenia Gravis in a Sample Population
George Pennington and Andrew Wilson, *Liverpool, England*

Lee M. Eaton Memorial Panel: What Is and What Is Not Myasthenia Gravis?
Chairman: Robert B. Aird, *San Francisco*

Fatigue Syndromes Suggesting Myasthenia Gravis
Robert S. Schwab and Henry R. Viets, *Boston*

Defect of Neuromuscular Conduction Occasionally Associated with Malignant Intrathoracic Tumors
Edward H. Lambert, Lee M. Eaton, and E. Douglas Rooke, *Rochester, Minn.*

Observations on the Value and Limitations of the Curare Test in the Differential Diagnosis of Myasthenia Gravis
Lewis P. Rowland, Henry Aranow, Jr., and Paul F. A. Hoefer, *New York City*

Recent Studies in Curare Sensitivity in Myasthenia Gravis and Related Neuromuscular Disorders
Donald W. Mulder, E. Douglas Rooke, and Lee M. Eaton, *Rochester, Minn.*

Mild or Atypical Myasthenic States
Joseph E. Tether, Jr., *Indianapolis*

Factors Contributing to Exacerbation

Myasthenic States and Disturbances of Thyroid Metabolism
Benjamin Boshes, *Chicago*

Some Aspects of Disturbed Metabolism in Myasthenia
Walter O. Klingman, *Galveston, Tex.*

The Lymphocyte Count in Myasthenia Gravis
Vincent P. Perlo, *Boston*

Pathology of Myasthenia Gravis

Studies in Myasthenia Gravis: Pathological Anatomy in Thirty-Two Consecutive Postmortem Cases
Gabriel Genkins and Harvey Mendelow, *New York City*

Sunday, April 19, 1959

Afternoon session: 2 P.M.

Moderator: George D. Gammon, *Philadelphia*

Panel: Drug Management of Myasthenia Gravis

Chairman: Kermit E. Osserman, *New York City*

The Structure-Action Relationship of Neostigmine Type Cholinesterase Inhibitors

Francis F. Foldes, Gertrude Van Hees, and John F. I. Zeedick, *Pittsburgh*

B. C. Substances

Paul F. A. Hoefer, Henry Aranow, Jr., and Lewis P. Rowland, *New York City*

The Effect of Various Organic Phosphate Anticholinesterase Agents on Serum and Red Cell Cholinesterase

J. Alfred Rider and Hugo C. Moeller, *San Francisco*

Phospholine Iodide: An Anticholinesterase of New Structure

Kermit E. Osserman, Elliott S. Cohen, and Gabriel Genkins, *New York City*

Thymectomy Panel

Chairman: Augustus S. Rose, *Los Angeles*

Evaluation and Results in 130 Thymectomies

Robert S. Schwab, *Boston*

Evaluation of Keynes' Large Series of Thymectomies

R. T. Ross, *Winnipeg, Man.*

Carotid Sinus Denervation Treatment

Physiological Concept of the Central Action of the Carotid Sinus

Pierre Passouant, *Montpellier, France*

Carotid Sinus Denervation

André Thevenard, *Paris*

Crisis

Christian Herrmann, Jr., *Los Angeles*

Summary: Current Trends

George D. Gammon, *Philadelphia*

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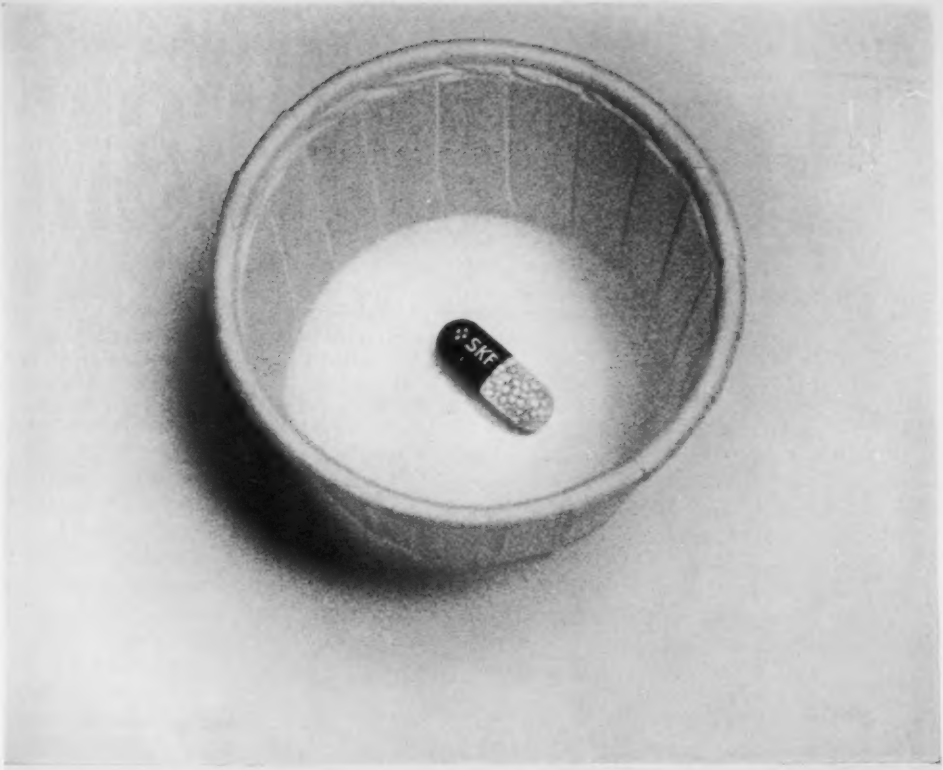

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MARCH 1959

New Diplomates in Neurology

At the December 15 and 16, 1958, examinations in New York of the American Board of Psychiatry and Neurology, nineteen candidates were certified in neurology. They are: Donald W. Baxter, Saskatoon, Sask.; J. Wallace Conklin, Providence; William E. DeMyer, Indianapolis; Pierre M. Dreyfus, Waverly, Mass.; Peter L. Eichman, Madison; H. William Gillen, Jackson, Miss.; William L. Harlan, Galveston; Ladislav P. Hinterbuchner, Brooklyn; Charles Kennedy, Philadelphia; Ralph C. Kennedy, Talmage, Calif.; Francis E. Kulcsar, Chapel Hill; John F. Kurtzke, Coatesville, Pa.; Lloyd J. Lemmen, Los Angeles; Herbert L. Martin, Burlington, Vt.; John C. Moench, New Haven; Joseph L. O'Brien, New York; Donald H. Osterberg, Cambridge; Stefan Shanzer, New York; Lever F. Stewart, Charlottesville, Va.....All communications relative to Board examinations should be sent to Dr. David A. Boyd, Jr., Secretary-Treasurer, 102-110 Second Avenue, Southwest, Rochester, Minn.

ANA To Meet in Atlantic City June 15-17

The Eighty-fourth Annual Meeting of the American Neurological Association will be held in the Claridge Hotel, Atlantic City, on Monday, Tuesday, and Wednesday, June 15-17, 1959. There will be a full day of scientific sessions on Monday, June 15, and Tuesday, June 16, and a morning session on Wednesday, June 17. The Annual Dinner will be held on Tuesday evening, June 16. Members of the Association wishing a place on the program should submit to the Secretary, before March 15, 1959, an abstract not exceeding two hundred words for the program and an abstract not exceeding one thousand words for the transactions. Nonmembers may read papers of special interest by invitation of the Program Committee. The papers presented at the meeting must be submitted for acceptance or rejection by the Editorial Board of the Archives of Neurology and Psychiatry, which is now the official journal of the ANA. Further information on the ANA program may be obtained from Dr. Charles Rupp, 133 South 36th Street, Philadelphia 4.

Forster Reports on Russian Neurologic Mission

AAN President, Francis M. Forster, Chairman of a neurologic exchange mission[1] to Russia, recently submitted a preliminary report of impressions and experiences perceived in the Soviet Union (November 18-December 18, 1958). The mission was organized

[1]Other members of the mission were Karl Frank, Louis S. Goodman, Henry W. Woltman, Clinton N. Woolsey, and Paul I. Yakovlev.

and sponsored by the National Institute of Neurological Diseases and Blindness in collaboration with the Public Health Service and the Department of State. Its purpose was to observe the nature and conduct of research activities in the physiology and pharmacology of the nervous system in the U.S.S.R....In his report, Forster touches on the training of Soviet physicians and scientists; the organization and orientation of their research; physical facilities and research equipment; types of research personnel; and a consideration of Soviet research and development. Among other things, Forster said, "Neurologic research is given the highest priority because of the Soviet concept that the central nervous system is the central control of all bodily processes and must be regarded as the ultimate target in biologic research." Among the Soviet methodologies that impressed the U.S. delegates were "the application of descriptive anatomy to research; active studies in developmental morphology, and in the phylogeny and ontogeny of the central and autonomic nervous systems; the preservation of a historical approach in the training of scientists which appears to provide a stimulating background for further achievement; and the acute awareness of Soviet scientists of things going on elsewhere and their determination to assimilate and improve them." Forster, near the end of his report, recommends "that research in the United States in neurophysiology and neuropharmacology be supported even more generously than it has been; that Soviet scientific literature in English translation be made more available to American scientists; that the program of scientific exchange missions be promoted further; and that a program of exchange fellowships be developed."....He adds a final note when he writes: "If one appreciates that the majority of Soviet research institutes are postwar in origin and that their application to modern research techniques is relatively recent, one cannot be complacent about their potential for rapid progress in the future." ....A return Russian mission[2] is now in progress in the United States.

New Training Programs Announced In Neuroanatomy and Neuropathology Louis Hausman of the Department of Anatomy of the New York University-Bellevue Medical Center announces that this Center is offering a three-month training fellowship with stipend in neuroanatomy and neurophysiology, beginning September 1959. Applications must be submitted before May 1, 1959 and inquiries should be forwarded to Dr. Hausman of the New York University-Bellevue Medical Center, 550 First Avenue, New York City 16....John A. Wagner, Professor of Neuropathology of the School of Medicine, University of Maryland, announces the activation of a new training program in neuropathology. The

[2]The members of the visiting Soviet team are S. V. Anichov (pharmacologist and physiologist specializing in the study of chemoreceptors); V. S. Rusinov (physiologist, specializing in electroencephalography and electroretinography); and V. V. Zakusov (pharmacologist and chemotherapist).

program is designed for Board-certified pathologists or those eligible for certification who wish to pursue an academic career in neuropathology. It is a two-year program aided by a grant from the National Institute of Neurological Diseases and Blindness.... All inquiries should be addressed to Professor Wagner at the University of Maryland School of Medicine, Baltimore 1.

Edwin Zabriskie Dies Edwin G. Zabriskie, 84, Professor Emeritus of clinical neurology at Columbia University, quietly passed away in the Columbia Presbyterian Medical Center, January 13, 1959. Dr. Zabriskie, or "the Colonel" as he was often called, stood out as the gentleman soldier and statesman of American neurology for more than a quarter of a century. The focus of his activities and affection was the New York Neurological Institute where he taught for over forty years, but he was beloved everywhere. A romanticist, a humanist with a warm heart, Dr. Zabriskie was a symbol of tender strength to his colleagues and patients and was always available. A member of New York's Century Club and San Francisco's Bohemian Club, he was an accomplished musician, maintaining a string quartet at a weekly winter meeting. A past President of the American Neurological Association, he also was a staunch supporter of the American Academy of Neurology. He will be missed greatly....A sister, Miss Louise G. Zabriskie and a nephew, Dr. John Barrea Zabriskie, now serving in the United States Air Force, survive.

Neurological Reunion To Be Held in Paris The Twenty-third Annual International Neurological Reunion, organized by the French Society of Neurology, will be held in Paris on Tuesday and Wednesday, June 2-3, 1959. The program, which will be devoted to a consideration of neurologic accidents resulting from modern medications, is under the direction of Professor P. Mollaret. The main topics comprise physiologic classifications, neurologic accidents arising from neuroepileptic medications, neuroendocrine therapy, and antibiotics, including their toxic effects on the cochleovestibular system....There will also be a program of free papers, the titles of which must be forwarded to the Secretary-General before the first of May for submission to the Program Committee. The International Reunion will be followed on Thursday, June 4, by the regular monthly scientific sessions of the Society....All members of the French Society of Neurology may participate in the International Reunion without the payment of a registration fee; however, Associate members and Honorary members of foreign title who wish to participate in the Reunion must register with the Secretary-General before May 1. French and foreign physicians who are not members of the Society may apply to the Secretary-General and may be admitted to the sessions upon the payment of a registration fee of 2,500 francs.

Registrations should be forwarded to the Secretary-General, Docteur J. Sigwald, 68 boulevard de Courcelles, Paris-XVII•.

WFN Receives Grant Awards The World Federation of Neurology is the recipient of two research grant awards from the National Institute of Neurological Diseases and Blindness. The first, an award of $12,000, is for aid in the organization and conduct by President Ludo van Bogaert of an international symposium on the neuropathology of the encephalitides. This symposium, to be held in Antwerp in early May 1959, will serve as a precursor for the development of an international reporting system and of standards of nomenclature for the classification of neurologic disease processes....The second award of $126,000 has been made to the Federation for the implementation of international research, especially in collaborative and cooperative studies in cerebrovascular disease and in perinatal neurologic deficits. These grants serve to activate the Federation's functions as a coordinating mechanism and a central clearing station for the stimulation, formulation, and integration of international research projects. Among the countries to join recently are Australia, Colombia, Greece, and Hungary. Inquiries should be sent to Dr. Ludo van Bogaert, 59 rue Philippe Williot, Antwerp, Belgium.

Center for Comparative Neuropathology Organizing in Switzerland At the University of Bern, a research center is in the making to bridge the gap between veterinary neurology and human neurology and to establish a systematic comparative neuropathology of spontaneous diseases of animals, both domesticated and wild. Heading this enterprise are R. Frankhauser, professor of animal neuropathology, and E. Frauchiger, professor of comparative neurology and alternate delegate (Switzerland) to the World Federation of Neurology. The project includes protracted clinical studies of domesticated wild animals suffering from neurologic disorders; complete postmortems; and the application of modern technics for the examination of cerebrospinal fluid in neuroradiology and in electroencephalography. The research also extends to studies of the embryology of the central nervous system and of spontaneous congenital cerebral malformations arising in the perinatal period. The Bern Institute of Comparative Neuropathology is also tooling up as an exchange center for the review and distribution of publications, histologic sections or paraffin blocs, photographs, and slides....This project furnishes another example of international cooperation through neurologic research. Here it concerns the United States and Switzerland, through sponsorship of the project by the National Institute of Neurological Diseases and Blindness and the Swiss National Funds for the Advancement of Scientific Research.

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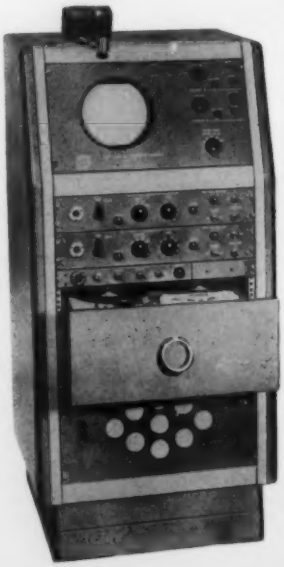

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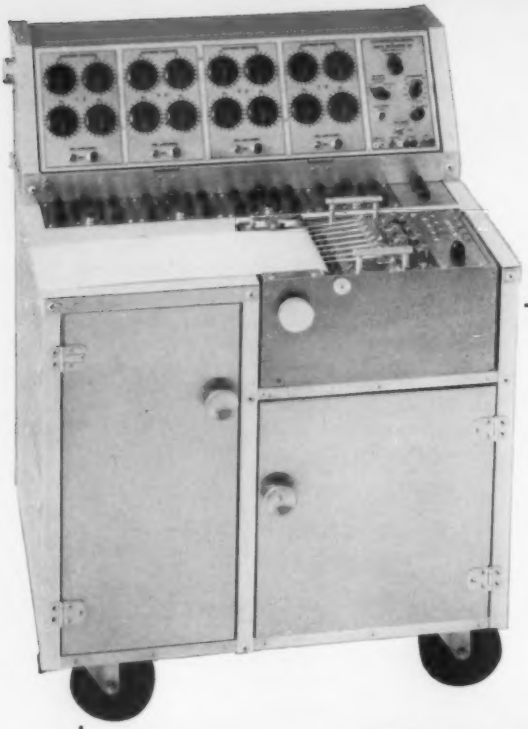

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IN HOSPITALIZED PSYCHIATRIC PATIENTS, Miltown has demonstrated great usefulness in relieving anxiety and tension.[1-5]

In tranquilizing effect Miltown has been found superior to phenothiazine derivatives and Rauwolfia products.[1] However, its anti-psychotic effect is less pronounced than that of the other drugs.[1]

On the other hand, combined with an effective anti-psychotic preparation, Miltown becomes "extremely valuable in alleviating the overactivity, tension, excitement and anxiety of the psychotic."[1]

An added advantage of Miltown is relaxation of skeletal muscle, not obtained with most other tranquilizers.

References: 1. Barsa, J. A.: Am. J. Psychiat. 115:79, July 1958. 2. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Connecticut M. J. 21:1047, Dec. 1957. 3. Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Ann. New York Acad. Sc. 67:789, May 9, 1957. 4. Pennington, V. M.: Am. J. Psychiat. 114:257, Sept. 1957. 5. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

Available in 400 mg. scored and 200 mg. sugar-coated tablets. Also available as MEPROSPAN* (200 mg. meprobamate *continuous release* capsules). *TRADE-MARK

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meprobamate (Wallace)

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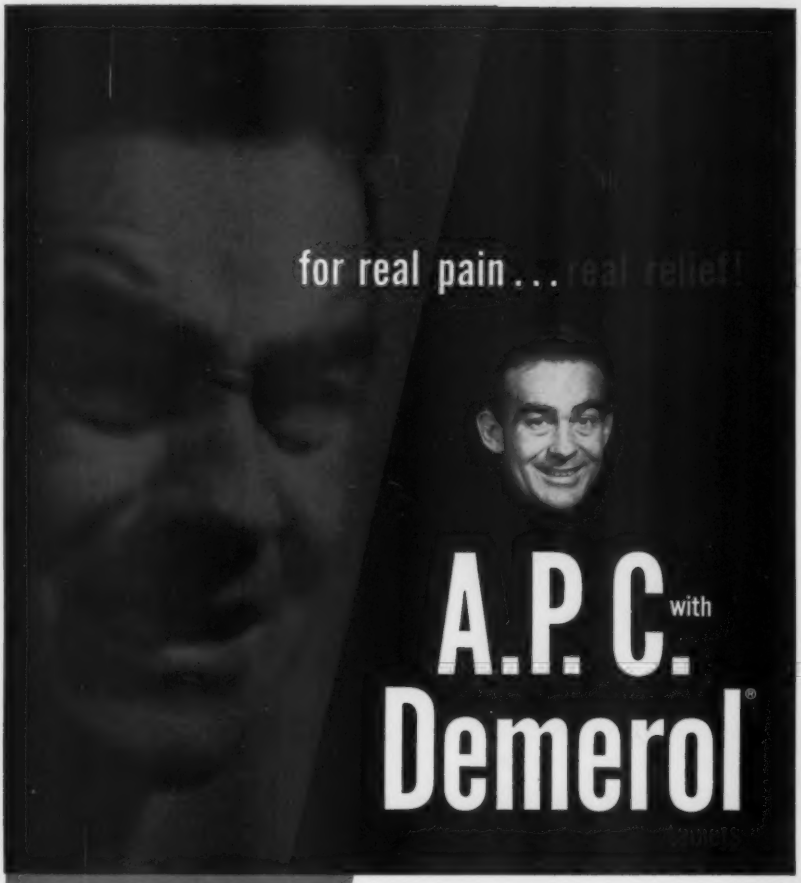

appreciably more effective than A.P.C. with codeine

or Codeine Substitutes

each tablet contains:

Aspirin	200 mg. (3 grains)
Phenacetin	150 mg. (2½ grains)
Caffeine	30 mg. (½ grain)
Demerol hydrochloride	30 mg. (½ grain)

adult dose: 1 or 2 tablets repeated in three or four hours as needed.

supplied: Bottles of 100 and 1000 tablets, scored.

Narcotic Blank Required.

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Demerol (brand of meperidine), trademark reg. U. S. Pat. Off.